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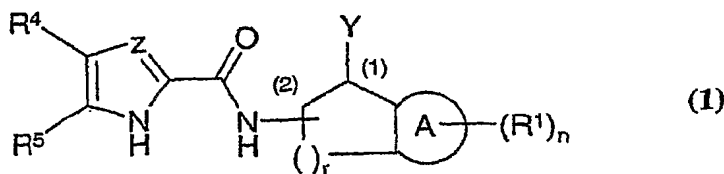
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(54) Title: HETEROCYCLIC AMIDE DERIVATIVES WHICH POSSESS GLYCOGEN PHOSPHORYLASE INHIBITORY ACTIVITY



(57) Abstract: A compound of the formula (1) or a pharmaceutically-acceptable salt, or pro-drug thereof; wherein, for example, Z is CH or nitrogen, R⁴ and R⁵ together are either -S-C(R⁶)=C(R⁷)- or -C(R⁷)=C(R⁶)-S-; R⁶ and R⁷ are independently selected from hydrogen, halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, carboxy and carbamoyl; A is phenylene or heteroarylene; n is 0, 1 or 2; r is 1 or 2; R¹ is halo, cyano or carboxy; Y is selected from -C(O)R², -C(O)OR², -C(O)NR²R³, -(1-4C)alkyl [optionally substituted] -(2-4C)alkenyl, -SO₂NR²R³, and -S(O)_cR² (wherein c is 0, 1 or 2); R² and R³ are independently selected from hydrogen, -O(1-4C)alkyl, -S(1-4C)alkyl, -N(1-4C)alkyl, heterocyclyl, aryl, and (1-4C)alkyl [optionally substituted]; possess glycogen phosphorylase inhibitory activity and accordingly have value in the treatment of disease states associated with increased glycogen phosphorylase activity. Processes for the manufacture of compounds and pharmaceutical compositions containing them are described.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

HETEROCYCLIC AMIDE DERIVATIVES WHICH POSSESS GLYCOGEN PHOSPHORYLASE INHIBITORY ACTIVITY

The present invention relates to heterocyclic amide derivatives, pharmaceutically acceptable salts and in-vivo hydrolysable esters thereof. These heterocyclic amides possess glycogen phosphorylase inhibitory activity and accordingly have value in the treatment of disease states associated with increased glycogen phosphorylase activity and thus are potentially useful in methods of treatment of a warm-blooded animal such as man. The invention also relates to processes for the manufacture of said heterocyclic amide derivatives, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments to inhibit glycogen phosphorylase activity in a warm-blooded animal such as man.

The liver is the major organ regulating glycaemia in the post-absorptive state. Additionally, although having a smaller role in the contribution to post-prandial blood glucose levels, the response of the liver to exogenous sources of plasma glucose is key to an ability to maintain euglycaemia. An increased hepatic glucose output (HGO) is considered to play an important role in maintaining the elevated fasting plasma glucose (FPG) levels seen in type 2 diabetics; particularly those with a FPG >140mg/dl (7.8mM). (Weyer et al, (1999), *J Clin Invest* 104: 787-794; Clore & Blackgard (1994), *Diabetes* 43: 256-262; De Fronzo, R. A., et al, (1992) *Diabetes Care* 15; 318 - 355; Reaven, G.M. (1995) *Diabetologia* 38; 3-13).

Since current oral, anti-diabetic therapies fail to bring FPG levels to within the normal, non-diabetic range and since raised FPG (and glycHbA1c) levels are risk factors for both macro- (Charles, M.A. et al (1996) *Lancet* 348, 1657-1658; Coutinho, M. et al (1999) *Diabetes Care* 22; 233-240; Shaw, J.E. et al (2000) *Diabetes Care* 23, 34-39) and micro-vascular disease (DCCT Research Group (1993) *New. Eng. J. Med.* 329; 977-986); the reduction and normalisation of elevated FPG levels remains a treatment goal in type 2 DM.

It has been estimated that, after an overnight fast, 74% of HGO was derived from glycogenolysis with the remainder derived from gluconeogenic precursors (Hellerstein et al (1997) *Am J Physiol*, 272: E163). Glycogen phosphorylase is a key enzyme in the generation by glycogenolysis of glucose-1-phosphate, and hence glucose in liver and also in other tissues such as muscle and neuronal tissue.

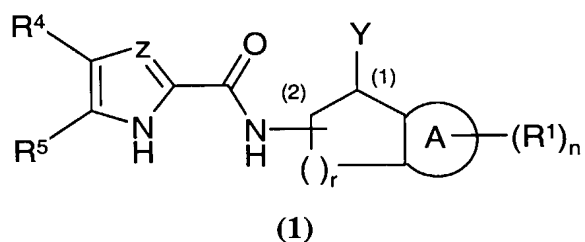
Liver glycogen phosphorylase activity is elevated in diabetic animal models including the db/db mouse and the fa/fa rat (Aiston S et al (2000). *Diabetologia* 43, 589-597).

Inhibition of hepatic glycogen phosphorylase with chloroindole inhibitors (CP91149 and CP320626) has been shown to reduce both glucagon stimulated glycogenolysis and glucose output in hepatocytes (Hoover et al (1998) J Med Chem 41, 2934-8; Martin et al (1998) PNAS 95, 1776-81). Additionally, plasma glucose concentration is reduced, in a dose related manner, db/db and ob/ob mice following treatment with these compounds.

Studies in conscious dogs with glucagon challenge in the absence and presence of another glycogen phosphorylase inhibitor, Bay K 3401, also show the potential utility of such agents where there is elevated circulating levels of glucagon, as in both Type 1 and Type 2 diabetes. In the presence of Bay R 3401, hepatic glucose output and arterial plasma glucose following a glucagon challenge were reduced significantly (Shiota et al, (1997), Am J Physiol, 273: E868).

The heterocyclic amides of the present invention possess glycogen phosphorylase inhibitory activity and accordingly are expected to be of use in the treatment of type 2 diabetes, insulin resistance, syndrome X, hyperinsulinaemia, hyperglucagonaemia, cardiac ischaemia and obesity, particularly type 2 diabetes.

According to one aspect of the present invention there is provided a compound of formula (1):



wherein:

Z is CH or nitrogen;

R⁴ and R⁵ together are either -S-C(R⁶)=C(R⁷)- or -C(R⁷)=C(R⁶)-S-;

R⁶ and R⁷ are independently selected from hydrogen, halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy and (1-4C)alkanoyl;

A is phenylene or heteroarylene;

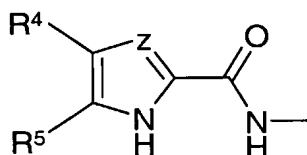
n is 0, 1 or 2;

R¹ is independently selected from halo, nitro, cyano, hydroxy, carboxy, carbamoyl,

N-(1-4C)alkylcarbamoyl, *N,N*-((1-4C)alkyl)₂carbamoyl, sulphamoyl, *N*-(1-4C)alkylsulphamoyl, *N,N*-((1-4C)alkyl)₂sulphamoyl, -S(O)_b(1-4C)alkyl (wherein b is 0, 1, or 2), -OS(O)₂(1-4C)alkyl, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, (1-4C)alkanoyl, (1-4C)alkanoyloxy, hydroxy(1-4C)alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy and -NHSO₂(1-4C)alkyl;

or, when n is 2, the two R¹ groups, together with the carbon atoms of A to which they are attached, may form a 4 to 7 membered saturated ring, optionally containing 1 or 2 heteroatoms independently selected from O, S and N, and optionally being substituted by one or two methyl groups;

r is 1 or 2; and when r is 1 the group



is a substituent on carbon (2) and when r is 2 (hereby forming a six membered ring) the same group is a substituent on carbon (2) or on carbon (3);

Y is selected from -C(O)R², -C(O)OR², -C(O)NR²R³, -(1-4C)alkyl [optionally substituted by 1 or 2 substituents independently selected from hydroxy, -C=NR², (1-4C)alkoxy, aryloxy, heterocycloxy, -S(O)_bR² (wherein b is 0, 1 or 2), -O-S(O)_bR² (wherein b is 0, 1 or 2), -NR²R³, -N(OH)R², -NR²C(=O)R², -NHOHC(=O)R², -SO₂NR²R³, -N(R²)SO₂R², aryl and heterocyclyl], -C(O)NOH, -C(O)NSH, -C(N)OH, -C(N)SH, -SO₂H, -SO₃H, -SO₂N(OH)R², -(2-4C)alkenyl, -SO₂NR²R³, -(1-4C)alkylC(O)R², -(1-4C)alkylC(O)OR², -(1-4C)alkylSC(O)R², -(1-4C)alkylOC(O)R², -(1-4C)alkylC(O)NR²R³, -(1-4C)alkylOC(O)OR², -(1-4C)alkylN(R²)C(O)OR², -(1-4C)alkylN(R²)C(O)NR²R³, -(1-4C)alkylOC(O)NR²R³, (3-6C)cycloalkyl (optionally substituted by 1 or 2 R⁸), aryl, heterocyclyl (wherein the heterocyclic ring is linked by a ring carbon atom), -(1-4C)alkylSO₂(2-4C)alkenyl and -S(O)_cR² (wherein c is 0, 1 or 2);

R² and R³ are independently selected from hydrogen, -O(1-4C)alkyl, -S(1-4C)alkyl, -N(1-4C)alkyl, heterocyclyl, aryl, and (1-4C)alkyl [optionally substituted by 1 or 2 R⁸ groups]; or

wherein NR²R³ may form a 4 to 7 membered saturated, partially saturated or unsaturated ring, optionally containing 1, 2 or 3 additional heteroatoms independently selected from N, O and S (provided there are no O-O, O-S or S-S bonds), wherein any -CH₂- may optionally be replaced

by $-C(=O)-$, and any N or S atom may optionally be oxidised to form an N-oxide or SO or SO_2 group respectively, and wherein the ring is optionally substituted by 1 or 2 substituents independently selected from halo, cyano, (1-4C)alkyl, hydroxy, (1-4C)alkoxy and (1-4C)alkylS(O)_b- (wherein b is 0, 1 or 2);

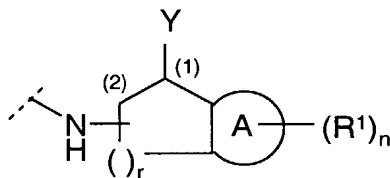
- 5 R^8 is independently selected from hydrogen, hydroxy, (1-4C)alkyl, (2-4C)alkenyl, (1-4C)alkoxy, cyano(1-4C)alkyl, amino(1-4C)alkyl [optionally substituted on nitrogen by 1 or 2 groups selected from (1-4C)alkyl, hydroxy, hydroxy(1-4C)alkyl, dihydroxy(1-4C)alkyl, $-CO_2(1-4C)alkyl$, aryl and aryl(1-4C)alkyl], halo(1-4C)alkyl, dihalo(1-4C)alkyl, trihalo(1-4C)alkyl, hydroxy(1-4C)alkyl, dihydroxy(1-4C)alkyl,
- 10 (1-4C)alkoxy(1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkoxy, 5- and 6-membered cyclic acetals and mono- and di-methyl derivatives thereof, aryl, heterocyclyl, heterocyclyl(1-4C)alkyl, (3-7C)cycloalkyl (optionally substituted with 1 or 2 hydroxy groups, (1-4C)alkyl or $-CO_2(1-4C)alkyl$), (1-4C)alkanoyl, (1-4C)alkylS(O)_b- (wherein b is 0, 1 or 2), (3-6C)cycloalkylS(O)_b- (wherein b is 0, 1 or 2), arylS(O)_b- (wherein b is 0, 1 or 2),
- 15 heterocyclylS(O)_b- (wherein b is 0, 1 or 2), benzylS(O)_b- (wherein b is 0, 1 or 2), (1-4C)alkylS(O)_c(1-4C)alkyl- (wherein c is 0, 1 or 2), $-N(OH)CHO$, $-C(=N-OH)NH_2$, $-C(=N-OH)NH(1-4C)alkyl$, $-C(=N-OH)N((1-4C)alkyl)_2$, $-C(=N-OH)NH(3-6C)cycloalkyl$, $-C(=N-OH)N((3-6C)cycloalkyl)_2$, $-COCOOR^9$, $-C(O)N(R^9)(R^{10})$, $-NHC(O)R^9$, $-C(O)NH SO_2((1-4C)alkyl)$, $-NH SO_2R^9$, $(R^9)(R^{10})NSO_2-$, $-COCH_2OR^{11}$, $-COCH_2OH$,
- 20 $(R^9)(R^{10})N-$, $-COOR^9$, $-CH_2OR^9$, $-CH_2COOR^9$, $-CH_2OCOR^9$, $-CH_2CH(CO_2R^9)OH$, $-CH_2C(O)NR^9R^{10}$, $-(CH_2)_wCH(NR^9R^{10})CO_2R^9$ (wherein w is 1, 2 or 3), and $-(CH_2)_wCH(NR^9R^{10})CO(NR^9R^{10})$ (wherein w is 1, 2 or 3);
- R^9 , R^9 , R^{10} and R^{10} are independently selected from hydrogen, hydroxy, (1-4C)alkyl (optionally substituted by 1 or 2 R^{11}), (2-4C)alkenyl, (3-7C)cycloalkyl (optionally substituted
- 25 by 1 or 2 hydroxy groups), cyano((1-4C))alkyl, trihalo(1-4C)alkyl, aryl, heterocyclyl, heterocyclyl(1-4C)alkyl, $-CO_2(1-4C)alkyl$; or
- R^9 and R^{10} together with the nitrogen to which they are attached, and/or R^9 and R^{10} together with the nitrogen to which they are attached, form a 4- to 6-membered ring where the ring is optionally substituted on carbon by 1 or 2 substituents independently selected from oxo,
- 30 hydroxy, carboxy, halo, nitro, cyano, carbonyl, (1-4C)alkoxy and heterocyclyl; or the ring may be optionally substituted on two adjacent carbons by $-O-CH_2-O-$ to form a cyclic acetal wherein one or both of the hydrogens of the $-O-CH_2-O-$ group may be replaced by a methyl;
- R^{11} is independently selected from (1-4C)alkyl and hydroxy(1-4C)alkyl;

or a pharmaceutically acceptable salt or pro-drug thereof.

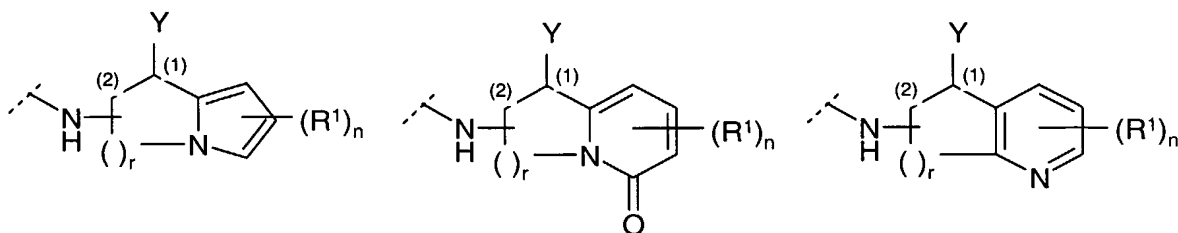
In a further aspect of the invention, there is provided a compound of the formula (1) as hereinbefore defined, or a pharmaceutically-acceptable salt, or in-vivo hydrolysable ester thereof, wherein Y is selected from $-\text{C}(\text{O})\text{R}^2$, $-\text{C}(\text{O})\text{OR}^2$, $-\text{C}(\text{O})\text{NR}^2\text{R}^3$, $-(1-4\text{C})\text{alkyl}$

- 5 [optionally substituted by 1 or 2 substituents independently selected from hydroxy, $-\text{C}=\text{NR}^2$, $(1-4\text{C})\text{alkoxy}$, aryloxy, heterocyclyloxy, $-\text{S}(\text{O})_b\text{R}^2$ (wherein b is 0, 1 or 2), $-\text{O}-\text{S}(\text{O})_b\text{R}^2$ (wherein b is 0, 1 or 2), $-\text{NR}^2\text{R}^3$, $-\text{N}(\text{OH})\text{R}^2$, $-\text{NR}^2\text{C}(\text{=O})\text{R}^2$, $-\text{NHOHC}(\text{=O})\text{R}^2$, $-\text{SO}_2\text{NR}^2\text{R}^3$, $-\text{N}(\text{R}^2)\text{SO}_2\text{R}^2$, aryl and heterocyclyl], $-\text{C}(\text{O})\text{NOH}$, $-\text{C}(\text{O})\text{NSH}$, $-\text{C}(\text{N})\text{OH}$, $-\text{C}(\text{N})\text{SH}$, $-\text{SO}_2\text{H}$, $-\text{SO}_3\text{H}$, $-\text{SO}_2\text{N}(\text{OH})\text{R}^2$, $-(2-4\text{C})\text{alkenyl}$, $-\text{SO}_2\text{NR}^2\text{R}^3$, $-(1-4\text{C})\text{alkylC}(\text{O})\text{R}^2$, $-(1-4\text{C})\text{alkylC}(\text{O})\text{OR}^2$, $-(1-4\text{C})\text{alkylOC}(\text{O})\text{R}^2$, $-(1-4\text{C})\text{alkylC}(\text{O})\text{NR}^2\text{R}^3$, $-(1-4\text{C})\text{alkylOC}(\text{O})\text{OR}^2$, $-(1-4\text{C})\text{alkylN}(\text{R}^2)\text{C}(\text{O})\text{OR}^2$, $-(1-4\text{C})\text{alkylN}(\text{R}^2)\text{C}(\text{O})\text{NR}^2\text{R}^3$, $-(1-4\text{C})\text{alkylOC}(\text{O})\text{NR}^2\text{R}^3$, $(3-6\text{C})\text{cycloalkyl}$ (optionally substituted by 1 or 2 R^8), aryl, heterocyclyl (wherein the heterocyclic ring is linked by a ring carbon atom), and $-\text{S}(\text{O})_c\text{R}^2$ (wherein c is 0, 1 or 2).

- 15 It is to be understood that when A is heteroarylene, the bridgehead atoms joining ring A to the ring may be heteroatoms. Therefore, for example, the definition of



when A is heteroarylene encompasses the structures:



20

It is to be understood that, where optional substitution on alkyl or cycloalkyl groups in Y, R^3 , R^9 and R^{10} (as defined hereinbefore or hereinafter) allows two hydroxy substituents on the alkyl or cycloalkyl group, or one hydroxy substituent and a second substituent linked by a heteroatom (for example alkoxy), then these two substituents are not substituents on the same

25 carbon atom of the alkyl or cycloalkyl group.

In another aspect, the invention relates to compounds of formula (1) as hereinabove defined or to a pharmaceutically acceptable salt.

In another aspect, the invention relates to compounds of formula (1) as hereinabove defined or to a pro-drug thereof. Suitable examples of pro-drugs of compounds of formula (1) are in-vivo hydrolysable esters of compounds of formula (1). Therefore in another aspect, the invention relates to compounds of formula (1) as hereinabove defined or to an in-vivo hydrolysable ester thereof.

It is to be understood that, insofar as certain of the compounds of formula (1) defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses glycogen phosphorylase inhibition activity. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, the above-mentioned activity may be evaluated using the standard laboratory techniques referred to hereinafter.

Within the present invention it is to be understood that a compound of the formula (1) or a salt thereof may exhibit the phenomenon of tautomerism and that the formulae drawings within this specification can represent only one of the possible tautomeric forms. It is to be understood that the invention encompasses any tautomeric form which has glycogen phosphorylase inhibition activity and is not to be limited merely to any one tautomeric form utilised within the formulae drawings. The formulae drawings within this specification can represent only one of the possible tautomeric forms and it is to be understood that the specification encompasses all possible tautomeric forms of the compounds drawn not just those forms which it has been possible to show graphically herein.

It is also to be understood that certain compounds of the formula (1) and salts thereof can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which have glycogen phosphorylase inhibition activity.

It is also to be understood that certain compounds of the formula (1) may exhibit polymorphism, and that the invention encompasses all such forms which possess glycogen phosphorylase inhibition activity.

The present invention relates to the compounds of formula (1) as hereinbefore defined as well as to the salts thereof. Salts for use in pharmaceutical compositions will be

pharmaceutically acceptable salts, but other salts may be useful in the production of the compounds of formula (1) and their pharmaceutically acceptable salts. Pharmaceutically acceptable salts of the invention may, for example, include acid addition salts of the compounds of formula (1) as hereinbefore defined which are sufficiently basic to form such salts. Such acid addition salts include for example salts with inorganic or organic acids affording pharmaceutically acceptable anions such as with hydrogen halides (especially hydrochloric or hydrobromic acid of which hydrochloric acid is particularly preferred) or with sulphuric or phosphoric acid, or with trifluoroacetic, citric or maleic acid. Suitable salts include hydrochlorides, hydrobromides, phosphates, sulphates, hydrogen sulphates, alkylsulphonates, arylsulphonates, acetates, benzoates, citrates, maleates, fumarates, succinates, lactates and tartrates. In addition where the compounds of formula (1) are sufficiently acidic, pharmaceutically acceptable salts may be formed with an inorganic or organic base which affords a pharmaceutically acceptable cation. Such salts with inorganic or organic bases include for example an alkali metal salt, such as a sodium or potassium salt, an alkaline earth metal salt such as a calcium or magnesium salt, an ammonium salt or for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

The compounds of the invention may be administered in the form of a pro-drug which is broken down in the human or animal body to give a compound of the invention. A prodrug may be used to alter or improve the physical and/or pharmacokinetic profile of the parent compound and can be formed when the parent compound contains a suitable group or substituent which can be derivatised to form a prodrug. Examples of pro-drugs include in-vivo hydrolysable esters of a compound of the invention or a pharmaceutically-acceptable salt thereof.

Various forms of prodrugs are known in the art, for examples see:

- a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);
- b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-191 (1991);
- c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);
- d) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77, 285 (1988); and
- e) N. Kakeya, *et al.*, Chem Pharm Bull, 32, 692 (1984).

An *in vivo* hydrolysable ester of a compound of formula (1) containing carboxy or hydroxy group is, for example. A pharmaceutically acceptable ester which is cleaved in the human or animal body to produce the parent acid or alcohol.

Suitable pharmaceutically acceptable esters for carboxy include (1-6C)alkoxymethyl
5 esters for example methoxymethyl, (1-6C)alkanoyloxymethyl esters for example
pivaloyloxymethyl, phthalidyl esters, (3-8C)cycloalkoxycarbonyloxy(1-6C)alkyl esters for
example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example
5-methyl-1,3-dioxolen-2-onylmethyl; and (1-6C)alkoxycarbonyloxyethyl esters for example
1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of
10 this invention.

Suitable pharmaceutically-acceptable esters for hydroxy include inorganic esters such
as phosphate esters (including phosphoramidic cyclic esters) and α -acyloxyalkyl ethers and
related compounds which as a result of the *in-vivo* hydrolysis of the ester breakdown to give
the parent hydroxy group/s. Examples of α -acyloxyalkyl ethers include acetoxymethoxy and
15 2,2-dimethylpropionyloxymethoxy. A selection of *in-vivo* hydrolysable ester forming groups
for hydroxy include (1-10C)alkanoyl, for example acetyl; benzoyl; phenylacetyl; substituted
benzoyl and phenylacetyl, (1-10C)alkoxycarbonyl (to give alkyl carbonate esters), for example
ethoxycarbonyl; di-((1-4C))alkylcarbamoyle and *N*-(di-((1-4C))alkylaminoethyl)-*N*-((1-
4C))alkylcarbamoyle (to give carbamates); di-((1-4C))alkylaminoacetyl and carboxyacetyl.
20 Examples of ring substituents on phenylacetyl and benzoyl include aminomethyl, ((1-
4C))alkylaminomethyl and di-(((1-4C))alkyl)aminomethyl, and morpholino or piperazino
linked from a ring nitrogen atom via a methylene linking group to the 3- or 4- position of the
benzoyl ring. Other interesting *in-vivo* hydrolysable esters include, for example, $R^A C(O)O((1-
6C))alkyl-CO-$, wherein R^A is for example, benzyloxy-((1-4C))alkyl, or phenyl). Suitable
25 substituents on a phenyl group in such esters include, for example, 4-((1-4C))piperazino-((1-
4C))alkyl, piperazino-((1-4C))alkyl and morpholino(1-4C)alkyl.

In this specification the generic term "alkyl" includes both straight-chain and
branched-chain alkyl groups. However references to individual alkyl groups such as "propyl"
30 are specific for the straight chain version only and references to individual branched-chain
alkyl groups such as *t*-butyl are specific for the branched chain version only. For example, "(1-
4C)alkyl" includes methyl, ethyl, propyl, isopropyl and *t*-butyl and examples of "(1-6C)alkyl"

include the examples of “(1-4C)alkyl” and additionally pentyl, 2,3-dimethylpropyl, 3-methylbutyl and hexyl. An analogous convention applies to other generic terms, for example “(2-4C)alkenyl” includes vinyl, allyl and 1-propenyl and examples of “(2-6C)alkenyl” include the examples of “(2-4C)alkenyl” and additionally 1-butenyl, 2-butenyl, 3-butenyl, 2-methylbut-2-enyl, 3-methylbut-1-enyl, 1-pentenyl, 3-pentenyl and 4-hexenyl. Examples of “(2-4C)alkynyl” includes ethynyl, 1-propynyl and 2-propynyl and examples of “(2-6C)alkynyl” include the examples of “(2-4C)alkynyl” and additionally 3-butyne, 2-pentyne and 1-methylpent-2-ynyl.

The term “hydroxy(1-4C)alkyl” includes hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxyisopropyl and hydroxybutyl. The term “hydroxyethyl” includes 1-hydroxyethyl and 2-hydroxyethyl. The term “hydroxypropyl” includes 1-hydroxypropyl, 2-hydroxypropyl and 3-hydroxypropyl and an analogous convention applies to terms such as hydroxybutyl. The term “dihydroxy(1-4C)alkyl” includes dihydroxyethyl, dihydroxypropyl, dihydroxyisopropyl and dihydroxybutyl. The term “dihydroxypropyl” includes 1,2-dihydroxypropyl and 1,3-dihydroxypropyl. An analogous convention applies to terms such as dihydroxyisopropyl and dihydroxybutyl.

The term “halo” refers to fluoro, chloro, bromo and iodo. The term “dihalo(1-4C)alkyl” includes difluoromethyl and dichloromethyl. The term “trihalo(1-4C)alkyl” includes trifluoromethyl.

Examples of “5- and 6-membered cyclic acetals and mono- and di-methyl derivatives thereof” are:

1,3-dioxolan-4-yl, 2-methyl-1,3-dioxolan-4-yl, 2,2-dimethyl-1,3-dioxolan-4-yl; 2,2-dimethyl-1,3-dioxan-4-yl; 2,2-dimethyl-1,3-dioxan-5-yl; 1,3-dioxan-2-yl.

Examples of “(1-4C)alkoxy” and “-O(1-4C)alkyl” include methoxy, ethoxy, propoxy and isopropoxy. Examples of “(1-6C)alkoxy” include the examples of “(1-4C)alkoxy” and additionally butyloxy, *t*-butyloxy, pentoxy and 1,2-(methyl)₂propoxy. Examples of “(1-4C)alkanoyl” include formyl, acetyl and propionyl. Examples of “(1-6C)alkanoyl” include the example of “(1-4C)alkanoyl” and additionally butanoyl, pentanoyl, hexanoyl and 1,2-(methyl)₂propionyl. Examples of “(1-4C)alkanoyloxy” and -CO₂(1-4C)alkyl include formyloxy, acetoxy and propionoxy. Examples of “(1-6C)alkanoyloxy” include the examples of “(1-4C)alkanoyloxy” and additionally butanoyloxy, pentanoyloxy, hexanoyloxy and 1,2-(methyl)₂propionoxy. Examples of “*N*-((1-4C)alkyl)amino” include methylamino and ethylamino. Examples of “*N*-((1-6C)alkyl)amino” include the examples of “*N*-((1-

4C)alkyl)amino” and additionally pentylamino, hexylamino and 3-methylbutylamino.

Examples of “*N,N*-((1-4C)alkyl)₂amino” include *N,N*-(methyl)₂amino, *N,N*-(ethyl)₂amino and *N*-ethyl-*N*-methylamino. Examples of “*N,N*-((1-6C)alkyl)₂amino” include the example of “*N,N*-((1-4C)alkyl)₂amino” and additionally *N*-methyl-*N*-pentylamino and *N,N*-

(pentyl)₂amino. Examples of “*N*-((1-4C)alkyl)carbamoyl” are methylcarbamoyl and

ethylcarbamoyl. Examples of “*N*-((1-6C)alkyl)carbamoyl” are the examples of “*N*-((1-4C)alkyl)carbamoyl” and additionally pentylcarbamoyl, hexylcarbamoyl and 1,2-

(methyl)₂propylcarbamoyl. Examples of “*N,N*-((1-4C)alkyl)₂carbamoyl” are *N,N*-

(methyl)₂carbamoyl, *N,N*-(ethyl)₂carbamoyl and *N*-methyl-*N*-ethylcarbamoyl. Examples of

“*N,N*-((1-6C)alkyl)₂carbamoyl” are the examples of “*N,N*-((1-4C)alkyl)₂carbamoyl” and additionally *N,N*-(pentyl)₂carbamoyl, *N*-methyl-*N*-pentylcarbamoyl and *N*-ethyl-*N*-

hexylcarbamoyl. Examples of “*N*-((1-4C)alkyl)sulphamoyl” are *N*-(methyl)sulphamoyl and

N-(ethyl)sulphamoyl. Examples of “*N*-((1-6C)alkyl)sulphamoyl” are the examples of “*N*-((1-4C)alkyl)sulphamoyl” and additionally *N*-pentylsulphamoyl, *N*-hexylsulphamoyl and 1,2-

(methyl)₂propylsulphamoyl. Examples of “*N,N*-((1-4C)alkyl)₂sulphamoyl” are

N,N-(methyl)₂sulphamoyl, *N,N*-(ethyl)₂sulphamoyl and *N*-(methyl)-*N*-(ethyl)sulphamoyl.

Examples of “*N,N*-((1-6C)alkyl)₂sulphamoyl” are the examples of “*N,N*-((1-4C)alkyl)₂sulphamoyl” and additionally *N,N*-(pentyl)₂sulphamoyl, *N*-methyl-*N*-

pentylsulphamoyl and *N*-ethyl-*N*-hexylsulphamoyl. Examples of -NHSO₂(1-4C)alkyl are

methylsulfonylamino, ethylsulfonylamino, propylsulfonylamino, isopropylsulfonylamino and

tert-butylsulfonylamino.

Examples of “cyano((1-4C))alkyl” are cyanomethyl, cyanoethyl and cyanopropyl.

Examples of “(5-7C)cycloalkyl” are cyclopentyl, cyclohexyl and cycloheptyl. Examples of

“(3-8C)cycloalkyl” and “(3-7C)cycloalkyl” include “(5-7C)cycloalkyl”, cyclopropyl,

cyclobutyl and cyclooctyl. Examples of “(3-6C)cycloalkyl” include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

The term “amino(1-4C)alkyl” includes aminomethyl, aminoethyl, aminopropyl, aminoisopropyl and aminobutyl. The term “aminoethyl” includes 1-aminoethyl and 2-

aminoethyl. The term “aminopropyl” includes 1-aminopropyl, 2-aminopropyl and 3-

aminopropyl and an analogous convention applies to terms such as aminoethyl and

aminobutyl.

Examples of “(1-4C)alkoxy(1-4C)alkoxy” are methoxymethoxy, ethoxymethoxy, ethoxyethoxy and methoxyethoxy. Examples of “hydroxy(1-4C)alkoxy” are hydroxyethoxy

and hydroxypropoxy. Examples of "hydroxypropoxy" are 1-hydroxypropoxy, 2-hydroxypropoxy and 3-hydroxypropoxy. Examples of "(1-4C)alkoxy(1-4C)alkyl" include methoxymethyl, ethoxymethyl, methoxyethyl, isopropoxymethyl, and tert-butoxymethyl.

Examples of "(1-4C)alkylS(O)_b (wherein b is 0,1 or 2)", "(1-4C)alkylS(O)_c (wherein c is 0 to 2)" and "(1-4C)alkylS(O)_d (wherein d is 0 to 2)", independently include methylthio, ethylthio, propylthio, methanesulphinyl, ethanesulphinyl, propanesulphinyl, mesyl, ethanesulphonyl, propanesulphonyl and isopropanesulphonyl. Examples of "(1-4C)alkylS(O)_b(1-4C)alkyl-" (wherein b is 0,1 or 2)" include methylsulfonylmethyl, methylsulfinylmethyl, methylthiomethyl, ethylsulfonylmethyl, ethylsulfinylmethyl and ethylthiomethyl.

Examples of "-(1-4C)alkylSO₂(2-4C)alkenyl" include vinylsulfonylmethyl, vinylsulfonylethyl, and allylsulfonylmethyl.

Examples of "(3-6C)cycloalkylS(O)_b (wherein b is 0,1 or 2)" include cyclopropylthio, cyclopropylsulphinyl, cyclopropylsulphonyl, cyclobutylthio, cyclobutylsulphinyl, cyclobutylsulphonyl, cyclopentylthio, cyclopentylsulphinyl and cyclopentylsulphonyl.

Examples of "arylS(O)_b (wherein b is 0,1 or 2)" include phenylthio, phenylsulphinyl and phenylsulfonyl. Examples of "benzylS(O)_b (wherein b is 0,1 or 2)" include benzylthio, benzylsulfinyl and benzylsulfonyl. Examples of "heterocyclylS(O)_b (wherein b is 0,1 or 2)" include pyridylthio, pyridylsulfinyl, pyridylsulfonyl, imidazolylthio, imidazolylsulfinyl, imidazolylsulfonyl, pyrimidinylthio, pyrimidinylsulfinyl, pyrimidinylsulfonyl, piperidylthio, piperidylsulfinyl and piperidylsulfonyl.

Examples of "(1-6C)alkoxycarbonyl" include methoxycarbonyl, ethoxycarbonyl, *n*- and *t*-butoxycarbonyl. Examples of "(1-6C)alkoxycarbonylamino" include methoxycarbonylamino, ethoxycarbonylamino, *n*- and *t*-butoxycarbonylamino. Examples of "(1-6C)alkylsulphonyl-*N*-((1-6C)alkyl)amino" include methylsulphonyl-*N*-methylamino, ethylsulphonyl-*N*-methylamino and propylsulphonyl-*N*-ethylamino. Examples of "(1-6C)alkylsulphonylamino" include methylsulphonylamino, ethylsulphonylamino and propylsulphonylamino. Examples of "(1-6C)alkanoylamino" include formamido, acetamido and propionylamino.

For the avoidance of doubt it is to be understood that where in this specification a group is qualified by 'hereinbefore defined' or 'defined hereinbefore' the said group encompasses the first occurring and broadest definition as well as each and all of the particular definitions for that group.

It is to be understood that where substituents contain two substituents on an alkyl chain, in which both are linked by a heteroatom (for example two alkoxy substituents), then these two substituents are not substituents on the same carbon atom of the alkyl chain.

It is to be understood that optional substituents on any group may be attached to any
5 available atom as appropriate unless otherwise specified, including heteroatoms provided that they are not thereby quaternised.

Within this specification composite terms are used to describe groups comprising more than one functionality such as $-(1-6C)alkylNHSO_2(1-6C)alkyl$. Such terms are to be interpreted in accordance with the meaning which is understood by a person skilled in the art
10 for each component part. For example $-(1-6)alkylNHSO_2(1-6C)alkyl$ includes $-methylaminosulphonylmethyl$, $-methylaminosulphonylethyl$, $-ethylaminosulphonylmethyl$, and $-propylaminosulphonylbutyl$.

Where optional substituents are chosen from "0, 1, 2 or 3" groups it is to be understood that this definition includes all substituents being chosen from one of the specified
15 groups or the substituents being chosen from two or more of the specified groups. An analogous convention applies to substituents chosen from "0, 1 or 2" groups and "1 or 2" groups.

Substituents may be present at any suitable position on, for example, an alkyl group. Therefore, hydroxy substituted $(1-6C)alkyl$ includes hydroxymethyl, 1-hydroxyethyl,
20 2-hydroxyethyl and 3-hydroxypropyl.

"Heterocyclyl" is a saturated, partially saturated or unsaturated, optionally substituted monocyclic ring containing 5 to 7 atoms of which 1, 2, 3 or 4 ring atoms are chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a $-CH_2-$ group can optionally be replaced by a $-C(O)-$ and a ring sulphur atom
25 may be optionally oxidised to form the S-oxide(s). Examples and suitable values of the term "heterocyclyl" are morpholino, morpholinyl, piperidino, piperidyl, pyridyl, pyranal, pyrrolyl, imidazolyl, thiazolyl, thienyl, dioxolanyl, thiadiazolyl, piperazinyl, isothiazolidinyl, triazolyl, tetrazolyl, pyrrolidinyl, 2-oxazolidinonyl, 5-isoxazolonyl, thiomorpholino, pyrrolinyl, homopiperazinyl, 3,5-dioxapiperidinyl, 3-oxopyrazolin-5-yl, tetrahydropyranal,
30 tetrahydrothiopyranal, 1-oxotetrahydrothiopyranal, 1,1-dioxotetrahydrothiopyranal, pyrimidyl, pyrazinyl, pyridazinyl, pyrazolyl, pyrazolinyl, isoxazolyl, 4-oxopyridyl, 2-oxopyrrolidyl, 4-oxothiazolidyl, furyl, thienyl, oxazolyl, and oxadiazolyl.

Suitably a "heterocyclyl" is morpholino, morpholinyl, piperidino, piperidyl, pyridyl, pyranyl, pyrrolyl, imidazolyl, thiazolyl, thienyl, thiadiazolyl, piperazinyl, isothiazolidinyl, 1,3,4-triazolyl, tetrazolyl, pyrrolidinyl, thiomorpholino, pyrrolinyl, homopiperazinyl, 3,5-dioxapiperidinyl, pyrimidyl, pyrazinyl, pyridazinyl, pyrazolyl, pyrazolinyl, isoxazolyl, 4-oxopyridyl, 2-oxopyrrolidyl, 4-oxothiazolidyl, furyl, thienyl, oxazolyl, 1,3,4-oxadiazolyl, and 1,2,4-oxadiazolyl.

Conveniently "heterocyclyl" is oxazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazolyl, tetrazolyl, thiazolyl, thiadiazolyl, pyridyl, imidazolyl, furyl, thienyl, morpholine, pyrimidyl, pyrazinyl, pyridazinyl, pyrazolyl, pyrazolinyl, and piperazinyl.

Suitable optional substituents for "heterocyclyl" as a saturated or partially saturated ring are 1, 2 or 3 substituents independently selected from halo, cyano, hydroxy, (1-4C)alkyl, (1-4C)alkoxy and (1-4C)alkylS(O)_b (wherein b is 0, 1 or 2). Further suitable substituents for "heterocyclyl" as a saturated or partially saturated ring are 1, 2 or 3 substituents independently selected from fluoro, chloro, cyano, hydroxy, methyl, ethyl, methoxy, methylthio, methylsulfinyl and methylsulfonyl.

Suitable optional substituents for "heterocyclyl" as an unsaturated ring are 1, 2 or 3 substituents independently selected from halo, cyano, nitro, amino, hydroxy, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylS(O)_b (wherein b is 0, 1 or 2), *N*-((1-4C)alkyl)amino and *N,N*-((1-4C)alkyl)₂amino. Further suitable optional substituents for "heterocyclyl" as an unsaturated ring are 1, 2 or 3 substituents independently selected from fluoro, chloro, cyano, nitro, amino, methylamino, dimethylamino, hydroxy, methyl, ethyl, methoxy, methylthio, methylsulfinyl and methylsulfonyl.

Examples of "heterocyclyl(1-4C)alkyl" are morpholinomethyl, morpholinethyl, morpholinylmethyl, morpholinylethyl, piperidinomethyl, piperidinoethyl, piperidylmethyl, piperidylethyl, imidazolylmethyl, imidazolylethyl, oxazolylmethyl, oxazolylethyl, 1,3,4-oxadiazolylmethyl, 1,2,4-oxadiazolylmethyl, 1,2,4-oxadiazolylethyl, pyridylmethyl, pyridylethyl, furylmethyl, furylethyl, (thienyl)methyl, (thienyl)ethyl, pyrazinylmethyl, pyrazinylethyl, piperazinylmethyl and piperazinylethyl.

Examples of "aryl" are optionally substituted phenyl and naphthyl.

Examples of "aryl(1-4C)alkyl" are benzyl, phenethyl, naphthylmethyl and naphthylethyl.

Suitable optional substituents for "aryl" groups are 1, 2 or 3 substituents independently selected from halo, cyano, nitro, amino, hydroxy, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylS(O)_b

(wherein b is 0, 1 or 2), *N*-((1-4C)alkyl)amino and *N,N*-((1-4C)alkyl)₂amino. Further suitable optional substituents for “aryl” groups are 1, 2 or 3 substituents independently selected from fluoro, chloro, cyano, nitro, amino, methylamino, dimethylamino, hydroxy, methyl, ethyl, methoxy, methylthio, methylsulfinyl and methylsulfonyl.

5 “Heteroarylene” is a diradical of a heteroaryl group. A heteroaryl group is an aryl, monocyclic ring containing 5 to 7 atoms of which 1, 2, 3 or 4 ring atoms are chosen from nitrogen, sulphur or oxygen. Examples of heteroarylene are oxazolylenes, oxadiazolylenes, pyridylenes, pyrimidinylens, imidazolylenes, triazolylenes, tetrazolylenes, pyrazinylens, pyridazinylens, pyrrolylenes, thienylens and furylenes.

10 Suitable optional substituents for heteroaryl groups, unless otherwise defined, are 1, 2 or 3 substituents independently selected from halo, cyano, nitro, amino, hydroxy, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkylS(O)_b (wherein b is 0, 1 or 2), *N*-((1-4C)alkyl)amino and *N,N*-((1-4C)alkyl)₂amino. Further suitable optional substituents for “heteroaryl” groups are 1, 2 or 3 substituents independently selected from fluoro, chloro, cyano, nitro, amino, methylamino, dimethylamino, hydroxy, methyl, ethyl, methoxy, methylthio, methylsulfinyl and methylsulfonyl.

20 Preferred values of A, Y, Z, R¹ to R¹¹, r and n are as follows. Such values may be used where appropriate with any of the definitions, claims, aspects or embodiments defined hereinbefore or hereinafter.

In one embodiment of the invention are provided compounds of formula (1), in an alternative embodiment are provided pharmaceutically-acceptable salts of compounds of formula (1), in a further alternative embodiment are provided in-vivo hydrolysable esters of compounds of formula (1), and in a further alternative embodiment are provided

25 pharmaceutically-acceptable salts of in-vivo hydrolysable esters of compounds of formula (1). In a further alternative embodiment are provided pro-drugs of compounds of formula (1) and in a still further alternative embodiment are provided pharmaceutically-acceptable salts of pro-drugs of compounds of formula (1).

Particular examples of in-vivo hydrolysable esters of compounds of the formula (1) are

30 such esters of compounds of the formula (1) wherein Y comprises a group containing a carboxy group. Suitable esters are those hereinbefore described for carboxy groups.

In one aspect of the present invention there is provided a compound of formula (1) as depicted above wherein Z is CH.

In another aspect of the invention Z is nitrogen.

In one aspect of the present invention there is provided a compound of formula (1) as depicted above wherein R⁴ and R⁵ are together -S-C(R⁶)=C(R⁷)-.

In another aspect of the invention R⁴ and R⁵ are together -C(R⁷)=C(R⁶)-S-.

5 In a further aspect of the invention, R⁶ and R⁷ are independently selected from hydrogen, halo or (1-6C)alkyl.

Preferably R⁶ and R⁷ are independently selected from hydrogen, chloro, bromo or methyl.

Particularly R^6 and R^7 are independently selected from hydrogen or chloro.

10 More particularly one of R^6 and R^7 is chloro.

In one embodiment, one of R⁶ and R⁷ is chloro and the other is hydrogen.

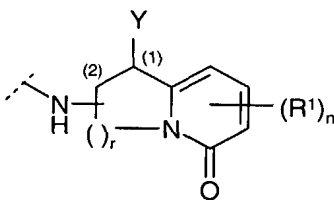
In another embodiment, both R⁶ and R⁷ are chloro.

In one aspect of the invention A is phenylene.

In another aspect of the invention A is heteroarylene.

15 Preferably A is selected from phenylene, pyridylene, pyrimidinylene, pyrrolylene, imidazolylene, triazolylene, tetrazolylene, oxazolylene, oxadiazolylene, thienylene and furylene.

In one embodiment, when A is heteroaryl, there is a nitrogen in a bridgehead position. In another embodiment, when A is heteroaryl, the heteroatoms are not in bridgehead positions. It will be appreciated that the preferred (more stable) bridgehead position is as shown below:



In one aspect of the invention n is 0 or 1.

In one aspect preferably n is 1.

25 In another aspect, preferably n is 0.

When n is 2, and the two R¹ groups, together with the carbon atoms of A to which they are attached, form a 4 to 7 membered saturated ring, optionally containing 1 or 2 heteroatoms independently selected from O, S and N, conveniently such a ring is a 5 or 6 membered ring. In one embodiment, such a 5 or 6 membered ring contains two O atoms (ie a cyclic acetal).

When the two R¹ groups together form such a cyclic acetal, preferably it is not substituted. Most preferably the two R¹ groups together are the group -O-CH₂-O-.

In another aspect of the present invention R¹ is selected from halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl and (1-4C)alkoxy.

- 5 In a further aspect R¹ is selected from halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, -S(O)_b(1-4C)alkyl (wherein b is 0, 1 or 2), -OS(O)₂(1-4C)alkyl, (1-4C)alkyl and (1-4C)alkoxy.

- 10 In a further aspect R¹ is selected from halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, -S(O)_bMe (wherein b is 0, 1 or 2), -OS(O)₂Me, methyl and methoxy.

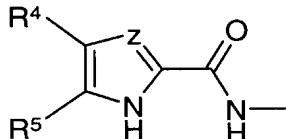
In a further aspect, R¹ is (1-4C)alkyl.

Preferably R¹ is selected from halo and (1-4C)alkoxy.

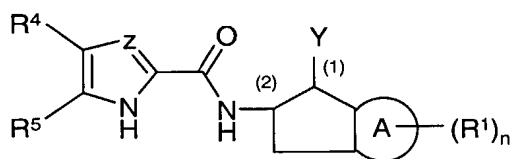
In another embodiment preferably R¹ is selected from fluoro, chloro, methyl, ethyl, methoxy and -O-CH₂-O-.

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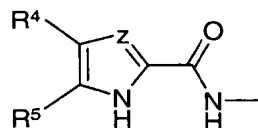
In one aspect of the invention r is 1 and when r is 1 the group



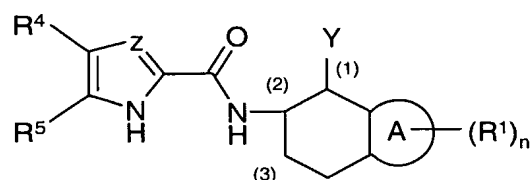
is a substituent on carbon (2) such that an example of when r is 1 is:



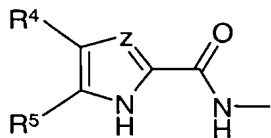
- 20 In another aspect of the invention r is 2 and when r is 2 the group



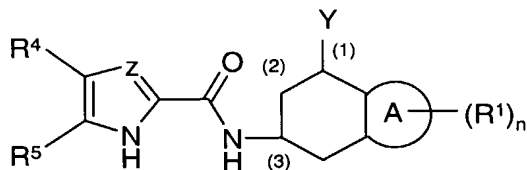
is a substituent on carbon (2) such that an example of when r is 2 is:



In another aspect of the invention r is 2 and when r is 2 the group



is a substituent on carbon (3) such that an example of when r is 2 is:



5

In one aspect, Y is selected from $-C(O)R^2$, $-C(O)OR^2$, $-C(O)NR^2R^3$, $-C(O)NOH$, $-C(O)NSH$, $-C(N)OH$, and $-C(N)SH$.

In another aspect, Y is selected from $-(1-4C)alkyl$ [optionally substituted by 1 or 2 substituents independently selected from hydroxy, $-C=NR^2$, $(1-4C)alkoxy$, aryloxy, heterocycloxy, $-S(O)_bR^2$ (wherein b is 0, 1 or 2), $-O-S(O)_bR^2$ (wherein b is 0, 1 or 2), $-NR^2R^3$, $-N(OH)R^2$, $-NR^2C(=O)R^2$, $-NHOHC(=O)R^2$, $-SO_2NR^2R^3$, $-N(R^2)SO_2R^2$, aryl and heterocyclyl], $-(2-4C)alkenyl$, $-(1-4C)alkylC(O)R^2$, $-(1-4C)alkylC(O)OR^2$, $-(1-4C)alkylOC(O)R^2$, $-(1-4C)alkylC(O)NR^2R^3$, $-(1-4C)alkylOC(O)OR^2$, $-(1-4C)alkylN(R^2)C(O)OR^2$, $-(1-4C)alkylN(R^2)C(O)NR^2R^3$, $-(1-4C)alkylOC(O)NR^2R^3$, $-(3-6C)cycloalkyl$ (optionally substituted by 1 or 2 R^8), aryl and heterocyclyl (wherein the heterocyclic ring is linked by a ring carbon atom).

In a further aspect Y is selected from $-SO_2H$, $-SO_3H$, $-SO_2N(OH)R^2$, $-SO_2NR^2R^3$ and $-S(O)_cR^2$ (wherein c is 0, 1 or 2).

In a further aspect, Y is selected from $-C(O)R^2$, $-C(O)OR^2$, $-C(O)NR^2R^3$, $-(1-4C)alkyl$ [optionally substituted by a substituent selected from hydroxy, $-C=NR^2$, $(1-4C)alkoxy$, aryloxy, heterocycloxy, $-S(O)_bR^2$ (wherein b is 0, 1 or 2), $-O-S(O)_bR^2$ (wherein b is 0, 1 or 2), $-NR^2R^3$, $-N(OH)R^2$, $-NR^2C(=O)R^2$, $-NHOHC(=O)R^2$, $-SO_2NR^2R^3$, $-N(R^2)SO_2R^2$, aryl and heterocyclyl], $-C(O)NOH$, $-C(O)NSH$, $-C(N)OH$, $-SO_2H$, $-SO_3H$, $-SO_2NR^2R^3$, $-(1-4C)alkylC(O)R^2$, $-(1-4C)alkylC(O)OR^2$, $-(1-4C)alkylSC(O)R^2$, $-(1-4C)alkylOC(O)R^2$, $-(1-4C)alkylC(O)NR^2R^3$, $-(1-4C)alkylOC(O)OR^2$, $-(1-4C)alkylN(R^2)C(O)OR^2$, $-(1-4C)alkylN(R^2)C(O)NR^2R^3$, $-(1-4C)alkylOC(O)NR^2R^3$, $-S(O)_cR^2$ (wherein c is 0, 1 or 2), aryl, heterocyclyl (wherein the heterocyclic ring is linked by a ring carbon atom) and $-(1-4C)alkylSO_2(2-4C)alkenyl$.

In a further aspect, Y is selected from $-C(O)R^2$, $-C(O)OR^2$, $-C(O)NR^2R^3$, $-(1-4C)alkyl$ [optionally substituted by a substituent selected from hydroxy, $-C=NR^2$, $(1-4C)alkoxy$, aryloxy, heterocycloxy, $-S(O)_bR^2$ (wherein b is 0, 1 or 2), $-O-S(O)_bR^2$ (wherein b is 0, 1 or 2), $-NR^2R^3$, $-N(OH)R^2$, $-NR^2C(=O)R^2$, $-NHOHC(=O)R^2$, $-SO_2NR^2R^3$,
 5 $-N(R^2)SO_2R^2$, aryl and heterocyclyl], $-C(O)NOH$, $-C(O)NSH$, $-C(N)OH$, $-SO_2H$, $-SO_3H$, $-SO_2NR^2R^3$, $-(1-4C)alkylC(O)R^2$, $-(1-4C)alkylC(O)OR^2$, $-(1-4C)alkylOC(O)R^2$, $-(1-4C)alkylC(O)NR^2R^3$, $-(1-4C)alkylOC(O)OR^2$, $-(1-4C)alkylN(R^2)C(O)OR^2$, $-(1-4C)alkylN(R^2)C(O)NR^2R^3$, $-(1-4C)alkylOC(O)NR^2R^3$, $-S(O)_cR^2$ (wherein c is 0, 1 or 2), aryl and heterocyclyl (wherein the heterocyclic ring is linked by a ring carbon atom).

10 In a further aspect, Y is selected from $-C(O)R^2$, $-C(O)OR^2$, $-C(O)NR^2R^3$, $-(1-4C)alkyl$ [optionally substituted by a substituent selected from hydroxy, $-C=NR^2$, $(1-4C)alkoxy$, aryloxy, heterocycloxy, $-S(O)_bR^2$ (wherein b is 0, 1 or 2), $-O-S(O)_bR^2$ (wherein b is 0, 1 or 2), $-NR^2R^3$, $-N(OH)R^2$, $-NR^2C(=O)R^2$, $-NHOHC(=O)R^2$, $-SO_2NR^2R^3$, $-N(R^2)SO_2R^2$, aryl and heterocyclyl], $-C(O)NOH$, $-C(O)NSH$, $-C(N)OH$, $-SO_2H$, $-SO_3H$,
 15 $-SO_2NR^2R^3$, $-(1-4C)alkylC(O)R^2$, $-(1-4C)alkylC(O)OR^2$, $-(1-4C)alkylSC(O)R^2$, $-(1-4C)alkylOC(O)R^2$, $-(1-4C)alkylC(O)NR^2R^3$, $-(1-4C)alkylOC(O)OR^2$, $-(1-4C)alkylN(R^2)C(O)OR^2$, $-(1-4C)alkylN(R^2)C(O)NR^2R^3$, $-(1-4C)alkylOC(O)NR^2R^3$, $-S(O)_cR^2$ (wherein c is 0, 1 or 2), aryl, heterocyclyl (wherein the heterocyclic ring is linked by a ring carbon atom) and $-(1-4C)alkylSO_2(2-4C)alkenyl$.

20 In a further aspect, Y is selected from $-C(O)R^2$, $-C(O)OR^2$, $-C(O)NR^2R^3$, $-(1-4C)alkyl$ [optionally substituted by a substituent selected from hydroxy, $-C=NR^2$, $(1-4C)alkoxy$, aryloxy, heterocycloxy, $-S(O)_bR^2$ (wherein b is 0, 1 or 2), $-O-S(O)_bR^2$ (wherein b is 0, 1 or 2), $-NR^2R^3$, $-N(OH)R^2$, $-NR^2C(=O)R^2$, $-NHOHC(=O)R^2$, $-SO_2NR^2R^3$, $-N(R^2)SO_2R^2$, aryl and heterocyclyl], $-C(O)NOH$, $-(1-4C)alkylC(O)R^2$,
 25 $-(1-4C)alkylC(O)OR^2$, $-(1-4C)alkylOC(O)R^2$, $-(1-4C)alkylC(O)NR^2R^3$, $-(1-4C)alkylOC(O)OR^2$, $-(1-4C)alkylN(R^2)C(O)OR^2$, $-(1-4C)alkylN(R^2)C(O)NR^2R^3$, $-(1-4C)alkylOC(O)NR^2R^3$, aryl and heterocyclyl (wherein the heterocyclic ring is linked by a ring carbon atom).

30 In a further aspect, Y is selected from $-C(O)R^2$, $-C(O)OR^2$, $-C(O)NR^2R^3$, $-(1-4C)alkyl$ [optionally substituted by a substituent selected from hydroxy, $-C=NR^2$, $(1-4C)alkoxy$, aryloxy, heterocycloxy, $-S(O)_bR^2$ (wherein b is 0, 1 or 2), $-O-S(O)_bR^2$ (wherein b is 0, 1 or 2), $-NR^2R^3$, $-N(OH)R^2$, $-NR^2C(=O)R^2$, $-NHOHC(=O)R^2$, $-SO_2NR^2R^3$, $-N(R^2)SO_2R^2$, aryl and heterocyclyl], $-C(O)NOH$, $-(1-4C)alkylC(O)R^2$,

-(1-4C)alkylC(O)OR², -(1-4C)alkylSC(O)R², -(1-4C)alkylOC(O)R²,
 -(1-4C)alkylC(O)NR²R³, -(1-4C)alkylOC(O)OR², -(1-4C)alkylN(R²)C(O)OR², -(1-
 4C)alkylN(R²)C(O)NR²R³, -(1-4C)alkylOC(O)NR²R³, aryl and heterocyclyl (wherein the
 heterocyclic ring is linked by a ring carbon atom) and -(1-4C)alkylSO₂(2-4C)alkenyl.

5 In a further aspect, Y is selected from -C(O)R², -C(O)OR², -C(O)NR²R³, -(1-
 4C)alkyl [optionally substituted by a substituent selected from hydroxy, (1-4C)alkoxy,
 aryloxy, heterocyclyloxy, -S(O)_bR² (wherein b is 0, 1 or 2), -O-S(O)_bR² (wherein b is 0, 1 or
 2), -NR²R³, -N(OH)R², -NR²C(=O)R², aryl and heterocyclyl], -C(O)NOH,
 -(1-4C)alkylC(O)R², -(1-4C)alkylC(O)OR², -(1-4C)alkylOC(O)R², -(1-4C)alkylC(O)NR²R³,
 10 -(1-4C)alkylOC(O)OR², -(1-4C)alkylN(R²)C(O)OR², -(1-4C)alkylN(R²)C(O)NR²R³,
 -(1-4C)alkylOC(O)NR²R³, aryl and heterocyclyl (wherein the heterocyclic ring is linked by a
 ring carbon atom).

In a further aspect, Y is selected from -C(O)R², -C(O)OR², -C(O)NR²R³, -(1-
 4C)alkyl [optionally substituted by a substituent selected from hydroxy, (1-4C)alkoxy,
 15 aryloxy, heterocyclyloxy, -S(O)_bR² (wherein b is 0, 1 or 2), -O-S(O)_bR² (wherein b is 0, 1 or
 2), -NR²R³, -N(OH)R², -NR²C(=O)R², aryl and heterocyclyl], -C(O)NOH,
 -(1-4C)alkylC(O)R², -(1-4C)alkylC(O)OR², -(1-4C)alkylSC(O)R², -(1-4C)alkylOC(O)R²,
 -(1-4C)alkylC(O)NR²R³, -(1-4C)alkylOC(O)OR², -(1-4C)alkylN(R²)C(O)OR², -(1-
 4C)alkylN(R²)C(O)NR²R³, -(1-4C)alkylOC(O)NR²R³, aryl and heterocyclyl (wherein the
 20 heterocyclic ring is linked by a ring carbon atom) and -(1-4C)alkylSO₂(2-4C)alkenyl.

In a further aspect, Y is selected from -C(O)R², -C(O)OR², -C(O)NR²R³, -C(O)NOH,
 and -(1-4C)alkyl [optionally substituted by a substituent selected from hydroxy, -S(O)_bR²
 (wherein b is 0, 1 or 2), -O-S(O)_bR² (wherein b is 0, 1 or 2), aryloxy, heterocyclyloxy,
 -NR²R³, -N(OH)R², -NR²C(=O)R², aryl and heterocyclyl].

25 In a further aspect, Y is selected from -C(O)R², -C(O)OR², -C(O)NR²R³, -C(O)NOH,
 and -(1-4C)alkyl [optionally substituted by a substituent selected from hydroxy, -S(O)_bR²
 (wherein b is 0, 1 or 2), -O-S(O)_bR² (wherein b is 0, 1 or 2), -NR²R³, -N(OH)R², and
 -NR²C(=O)R²].

In a further aspect, Y is selected from -C(O)R², -C(O)OR², -C(O)NR²R³, -C(O)NOH,
 30 and -(1-4C)alkyl [optionally substituted by a -NR²C(=O)R²], -(1-4C)alkylC(O)R²,
 -(1-4C)alkylC(O)OR², -(1-4C)alkylOC(O)R², -(1-4C)alkylC(O)NR²R³,
 -(1-4C)alkylOC(O)OR², -(1-4C)alkylN(R²)C(O)OR², -(1-4C)alkylN(R²)C(O)NR²R³,
 and -(1-4C)alkylOC(O)NR²R³.

In a further aspect, Y is selected from $-C(O)R^2$, $-C(O)OR^2$, $-C(O)NR^2R^3$, $-C(O)NOH$, and $-(1-4C)alkyl$ [optionally substituted by a $-NR^2C(=O)R^2$], $-(1-4C)alkylC(O)R^2$, $-(1-4C)alkylC(O)OR^2$, $-(1-4C)alkylSC(O)R^2$, $-(1-4C)alkylOC(O)R^2$, $-(1-4C)alkylC(O)NR^2R^3$, $-(1-4C)alkylOC(O)OR^2$, $-(1-4C)alkylN(R^2)C(O)OR^2$,
 5 $-(1-4C)alkylN(R^2)C(O)NR^2R^3$, $-(1-4C)alkylSO_2(2-4C)alkenyl$ and $-(1-4C)alkylOC(O)NR^2R^3$.

In one aspect R^2 and R^3 are independently selected from hydrogen, $-O(1-4C)alkyl$, $-S(1-4C)alkyl$, and $-N(1-4C)alkyl$.

In one aspect R^2 and R^3 are independently selected from hydrogen, $-O(1-4C)alkyl$ and $-N(1-4C)alkyl$.

10 In another aspect R^2 and R^3 are independently selected from hydrogen, heterocyclyl, aryl and $(1-4C)alkyl$ [optionally substituted by 1 or 2 R^8 groups].

In a further aspect R^2 and R^3 are independently selected from hydrogen and $(1-4C)alkyl$ [optionally substituted by 1 or 2 R^8 groups].

In another aspect an NR^2R^3 group forms a 4 to 7 membered saturated, partially
 15 saturated or unsaturated ring, optionally containing 1, 2 or 3 additional heteroatoms independently selected from N, O and S, wherein any $-CH_2-$ may optionally be replaced by $-C(=O)-$, and any N or S atom may optionally be oxidised to form an N-oxide or SO or SO_2 group respectively, and wherein the ring is optionally substituted by 1 or 2 substituents independently selected from halo, cyano, $(1-4C)alkyl$, hydroxy, $(1-4C)alkoxy$ and $(1-4C)alkylS(O)_b-$ (wherein b is 0, 1 or 2).
 20

In another aspect an NR^2R^3 group forms a 5 or 6 membered saturated, partially saturated or unsaturated ring, optionally containing 1, 2 or 3 additional heteroatoms independently selected from N, O and S, wherein any $-CH_2-$ may optionally be replaced by $-C(=O)-$, and any N or S atom may optionally be oxidised to form an N-oxide or SO or SO_2
 25 group respectively, and wherein the ring is optionally substituted by 1 or 2 substituents independently selected from halo, cyano, $(1-4C)alkyl$, hydroxy, $(1-4C)alkoxy$ and $(1-4C)alkylS(O)_b-$ (wherein b is 0, 1 or 2). Suitably, such rings are selected from morpholine, thiomorpholine (and oxidised versions thereof), pyrrolidine, dihydropyridine, tetrahydropyridine, piperazine, piperidine.

30 Suitable optional substituents for a ring comprising NR^2R^3 are 1 or 2 substituents independently selected from halo, hydroxy and $(1-4C)alkoxy$. In one aspect the ring has 2 substituents and they are both hydroxy. In one aspect the ring has 2 substituents and they are both halo, particularly both are fluoro.

In another aspect, a ring comprising NR^2R^3 contains an additional ring atom selected from O, N and S. In another aspect, an additional sulphur atom is oxidised to form an S=O or SO_2 group.

In a further aspect R^2 and R^3 are independently selected from hydrogen, -O(1-4C)alkyl, -N(1-4C)alkyl, (1-4C)alkyl [optionally substituted by 1 or 2 R^8 groups]; or an NR^2R^3 group forms a 5 or 6 membered saturated, partially saturated or unsaturated ring, optionally containing 1, 2 or 3 additional heteroatoms independently selected from N, O and S, wherein any $-\text{CH}_2-$ may optionally be replaced by $-\text{C}(=\text{O})-$, and any N or S atom may optionally be oxidised to form an N-oxide or SO or SO_2 group respectively, and wherein the ring is optionally substituted by 1 or 2 substituents independently selected from halo, cyano, (1-4C)alkyl, hydroxy, (1-4C)alkoxy and (1-4C)alkylS(O)_b- (wherein b is 0, 1 or 2).

In a further aspect R^2 and R^3 are independently selected from hydrogen, -O(1-4C)alkyl, -N(1-4C)alkyl, (1-4C)alkyl [optionally substituted by 1 or 2 R^8 groups]; or an NR^2R^3 group forms a 5 or 6 membered saturated, partially saturated or unsaturated ring, optionally containing 1 or 2 additional heteroatoms independently selected from N, O and S, wherein any $-\text{CH}_2-$ may optionally be replaced by $-\text{C}(=\text{O})-$, and any N or S atom may optionally be oxidised to form an N-oxide or SO or SO_2 group respectively, and wherein the ring is optionally substituted by 1 or 2 substituents independently selected from halo, hydroxy and (1-4C)alkoxy.

In a further aspect R^2 and R^3 are independently selected from hydrogen, -O(1-4C)alkyl, -N(1-4C)alkyl, (1-4C)alkyl [optionally substituted by 1 or 2 R^8 groups]; or an NR^2R^3 group forms morpholine, thiomorpholine (and oxidised versions thereof), pyrrolidine, dihydropyridine, tetrahydropyridine, piperazine, piperidine ring and wherein the ring is optionally substituted by 1 or 2 substituents independently selected from halo, hydroxy and (1-4C)alkoxy.

In a further aspect R^2 and R^3 are independently selected from hydrogen, -O(1-4C)alkyl, -N(1-4C)alkyl, (1-4C)alkyl [optionally substituted by 1 or 2 R^8 groups]; or an NR^2R^3 group forms a morpholine, thiomorpholine (and oxidised versions thereof), pyrrolidine, or piperidine ring and wherein the ring is optionally substituted by 1 or 2 substituents independently selected from chloro, fluoro, hydroxy and methoxy;

In one aspect R^8 is independently selected from hydrogen, hydroxy, (1-4C)alkyl, (1-4C)alkoxy, cyano(1-4C)alkyl, amino(1-4C)alkyl [optionally substituted on nitrogen by 1 or 2 groups selected from (1-4C)alkyl, hydroxy, hydroxy(1-4C)alkyl,

dihydroxy(1-4C)alkyl, $-\text{CO}_2(1-4\text{C})\text{alkyl}$, aryl and aryl(1-4C)alkyl], halo(1-4C)alkyl, dihalo((1-4C)alkyl, trihalo(1-4C)alkyl, hydroxy(1-4C)alkyl, dihydroxy((1-4C))alkyl, (1-4C)alkoxy(1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkoxy, 5- and 6-membered cyclic acetals and mono- and di-methyl derivatives thereof, aryl, heterocyclyl, heterocyclyl(1-4C)alkyl, (1-4C)alkanoyl, (1-4C)alkylS(O)_b- (wherein b is 0, 1 or 2, (1-4C)alkylS(O)_c(1-4C)alkyl- (wherein c is 0, 1 or 2), $-\text{N}(\text{OH})\text{CHO}$, $-\text{COCOOR}^9$, $-\text{C}(\text{O})\text{N}(\text{R}^9)(\text{R}^{10})$, $-\text{NHC}(\text{O})\text{R}^9$, $-\text{C}(\text{O})\text{NHSO}_2(1-4\text{C})\text{alkyl}$, $-\text{NHSO}_2\text{R}^9$, $(\text{R}^9)(\text{R}^{10})\text{NSO}_2-$, $-\text{COCH}_2\text{OR}^{11}$, $-\text{COCH}_2\text{OH}$, $(\text{R}^9)(\text{R}^{10})\text{N}-$, $-\text{COOR}^9$, $-\text{CH}_2\text{OR}^9$, $-\text{CH}_2\text{COOR}^9$, $-\text{CH}_2\text{OCOR}^9$, $-\text{CH}_2\text{CH}(\text{CO}_2\text{R}^9)\text{OH}$, $-\text{CH}_2\text{C}(\text{O})\text{NR}^9\text{R}^{10}$, $-(\text{CH}_2)_w\text{CH}(\text{NR}^9\text{R}^{10})\text{CO}_2\text{R}^9$ (wherein w is 1, 2 or 3), and $-(\text{CH}_2)_w\text{CH}(\text{NR}^9\text{R}^{10})\text{CO}(\text{NR}^9\text{R}^{10})$ (wherein w is 1, 2 or 3).

In another aspect, R^8 is independently selected from hydrogen, hydroxy, (1-4C)alkyl, (1-4C)alkoxy, amino(1-4C)alkyl, halo(1-4C)alkyl, dihalo(1-4C)alkyl, trihalo(1-4C)alkyl, hydroxy(1-4C)alkyl, dihydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkoxy, (1-4C)alkanoyl, (1-4C)alkylS(O)_b- (wherein b is 0, 1 or 2, (1-4C)alkylS(O)_c(1-4C)alkyl- (wherein c is 0, 1 or 2), $-\text{N}(\text{OH})\text{CHO}$, $-\text{COCOOR}^9$, $-\text{C}(\text{O})\text{N}(\text{R}^9)(\text{R}^{10})$, $-\text{NHC}(\text{O})\text{R}^9$, $-\text{C}(\text{O})\text{NHSO}_2((1-4\text{C})\text{alkyl})$, $-\text{NHSO}_2\text{R}^9$, $(\text{R}^9)(\text{R}^{10})\text{NSO}_2-$, $-\text{COCH}_2\text{OR}^{11}$, $-\text{COCH}_2\text{OH}$, $(\text{R}^9)(\text{R}^{10})\text{N}-$, $-\text{COOR}^9$, $-\text{CH}_2\text{OR}^9$, $-\text{CH}_2\text{COOR}^9$ and $-\text{CH}_2\text{OCOR}^9$.

In another aspect, R^8 is independently selected from hydrogen, hydroxy, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkanoyl, $-\text{COCOOR}^9$, $-\text{C}(\text{O})\text{N}(\text{R}^9)(\text{R}^{10})$, $-\text{NHC}(\text{O})\text{R}^9$, $-\text{N}(\text{OH})\text{CHO}$, $-\text{C}(\text{O})\text{NHSO}_2(1-4\text{C})\text{alkyl}$, $-\text{NHSO}_2\text{R}^9$, $(\text{R}^9)(\text{R}^{10})\text{NSO}_2-$, $-\text{COCH}_2\text{OR}^{11}$, $-\text{COCH}_2\text{OH}$, $(\text{R}^9)(\text{R}^{10})\text{N}-$, $-\text{COOR}^9$, $-\text{CH}_2\text{OR}^9$, $-\text{CH}_2\text{COOR}^9$ and $-\text{CH}_2\text{OCOR}^9$.

In another aspect, R^8 is independently selected from hydrogen, hydroxy, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkanoyl, $-\text{COCOOR}^9$, $-\text{C}(\text{O})\text{N}(\text{R}^9)(\text{R}^{10})$, $-\text{NHC}(\text{O})\text{R}^9$, $-\text{N}(\text{OH})\text{CHO}$, $-\text{COOR}^9$, $-\text{CH}_2\text{OR}^9$, $-\text{CH}_2\text{COOR}^9$ and $-\text{CH}_2\text{OCOR}^9$.

In one aspect R^9 and R^{10} are independently selected from hydrogen, hydroxy and (1-4C)alkyl optionally substituted by 1 or 2 R^{11} .

Suitably R^{11} is (1-4C)alkyl.

In one aspect of the invention is provided a compound of the formula (I), or a pharmaceutically acceptable salt or pro-drug thereof, wherein

A is phenylene;

n is 0, 1 or 2;

Z is nitrogen;

R^4 and R^5 are together $-S-C(R^6)=C(R^7)-$ or $-C(R^7)=C(R^6)-S-$;

R^6 and R^7 are independently selected from hydrogen, chloro, bromo or methyl;

R^1 is selected from fluoro, chloro, methyl, ethyl, methoxy and $-O-CH_2-O-$;

Y is selected from $-C(O)R^2$, $-C(O)OR^2$, $-C(O)NR^2R^3$, $-(1-4C)alkyl$ [optionally substituted

5 by 1 or 2 substituents independently selected from hydroxy, $-C=NR^2$, $(1-4C)alkoxy$, aryloxy, heterocycloxy, $-S(O)_bR^2$ (wherein b is 0, 1 or 2), $-O-S(O)_bR^2$ (wherein b is 0, 1 or 2), $-NR^2R^3$, $-N(OH)R^2$, $-NR^2C(=O)R^2$, $-NHOHC(=O)R^2$, $-SO_2NR^2R^3$, $-N(R^2)SO_2R^2$, aryl and heterocyclyl], $-C(O)NOH$, $-C(O)NSH$, $-C(N)OH$, $-SO_2H$, $-SO_3H$, $-SO_2NR^2R^3$, $-(1-4C)alkylC(O)R^2$, $-(1-4C)alkylC(O)OR^2$, $-(1-4C)alkylOC(O)R^2$,
10 $-(1-4C)alkylC(O)NR^2R^3$, $-(1-4C)alkylOC(O)OR^2$, $-(1-4C)alkylN(R^2)C(O)OR^2$, $-(1-4C)alkylN(R^2)C(O)NR^2R^3$, and $-(1-4C)alkylOC(O)NR^2R^3-S(O)_cR^2$ (wherein c is 0, 1 or 2), aryl and heterocyclyl (wherein the heterocyclic ring is linked by a ring carbon atom);

R^2 and R^3 are independently selected from hydrogen, $-O(1-4C)alkyl$, $-N(1-4C)alkyl$, $(1-4C)alkyl$ [optionally substituted by 1 or 2 R^8 groups]; or an NR^2R^3 group forms a 5 or 6

15 membered saturated, partially saturated or unsaturated ring, optionally containing 1, 2 or 3 additional heteroatoms independently selected from N, O and S, wherein any $-CH_2-$ may optionally be replaced by $-C(=O)-$, and any N or S atom may optionally be oxidised to form an N-oxide or SO or SO_2 group respectively, and wherein the ring is optionally substituted by 1 or 2 substituents independently selected from halo, cyano, $(1-4C)alkyl$, hydroxy, $(1-4C)alkoxy$ and $(1-4C)alkylS(O)_b-$ (wherein b is 0, 1 or 2);
20

R^8 is independently selected from hydrogen, hydroxy, $(1-4C)alkyl$,

$(1-4C)alkoxy$, amino $(1-4C)alkyl$, halo $(1-4C)alkyl$, dihalo $(1-4C)alkyl$, trihalo $(1-4C)alkyl$, hydroxy $(1-4C)alkyl$, dihydroxy $(1-4C)alkyl$,

$(1-4C)alkoxy(1-4C)alkoxy$, $(1-4C)alkoxy(1-4C)alkyl$, hydroxy $(1-4C)alkoxy$, $(1-4C)alkanoyl$,

25 $(1-4C)alkylS(O)_b-$ (wherein b is 0, 1 or 2), $(1-4C)alkylS(O)_c(1-4C)alkyl$ (wherein c is 0, 1 or 2), $-N(OH)CHO$, $-COCOOR^9$, $-C(O)N(R^9)(R^{10})$, $-NHC(O)R^9$, $-C(O)NHSO_2(1-4C)alkyl$, $-NHSO_2R^9$, $(R^9)(R^{10})NSO_2-$, $-COCH_2OR^{11}$, $-COCH_2OH$, $(R^9)(R^{10})N-$, $-COOR^9$, $-CH_2OR^9$, $-CH_2COOR^9$ and $-CH_2OCOR^9$;

R^9 and R^{10} are independently selected from hydrogen, hydroxy and $(1-4C)alkyl$ optionally substituted by 1 or 2 R^{11});
30

R^{11} is $(1-4C)alkyl$.

In a further aspect of the invention, is provided a compound of the formula (I) or a pharmaceutically acceptable salt or pro-drug thereof, wherein

A is phenylene;

n is 0, 1 or 2;

5 R^1 is selected from fluoro, chloro, methyl, ethyl, methoxy and $-O-CH_2-O-$;

Z is nitrogen;

R^4 and R^5 are together $-S-C(R^6)=C(R^7)-$ or $-C(R^7)=C(R^6)-S-$;

R^6 and R^7 are independently selected from hydrogen, chloro, bromo or methyl;

10 Y is selected from $-C(O)R^2$, $-C(O)OR^2$, $-C(O)NR^2R^3$, $-(1-4C)alkyl$ [optionally substituted by a substituent selected from hydroxy, $(1-4C)alkoxy$, aryloxy, heterocycloxy, $-S(O)_bR^2$ (wherein b is 0, 1 or 2), $-O-S(O)_bR^2$ (wherein b is 0, 1 or 2), $-NR^2R^3$, $-N(OH)R^2$, $-NR^2C(=O)R^2$, aryl and heterocyclyl], $-C(O)NOH$, $-(1-4C)alkylC(O)R^2$, $-(1-4C)alkylC(O)OR^2$, $-(1-4C)alkylOC(O)R^2$, $-(1-4C)alkylC(O)NR^2R^3$, $-(1-4C)alkylOC(O)OR^2$, $-(1-4C)alkylN(R^2)C(O)OR^2$, $-(1-4C)alkylN(R^2)C(O)NR^2R^3$,
15 and $-(1-4C)alkylOC(O)NR^2R^3$ aryl and heterocyclyl (wherein the heterocyclic ring is linked by a ring carbon atom);

R^2 and R^3 are independently selected from hydrogen, $-O(1-4C)alkyl$, $-N(1-4C)alkyl$, $(1-4C)alkyl$ [optionally substituted by 1 or 2 R^8 groups]; or an NR^2R^3 group forms a morpholine, thiomorpholine (and oxidised versions thereof), pyrrolidine, dihydropyridine,

20 tetrahydropyridine, piperazine or piperidine ring and wherein the ring is optionally substituted by 1 or 2 substituents independently selected from halo, hydroxy and $(1-4C)alkoxy$;

R^8 is independently selected from hydrogen, hydroxy, $(1-4C)alkyl$,

$(1-4C)alkoxy$, $(1-4C)alkanoyl$, $-COCOOR^9$, $-C(O)N(R^9)(R^{10})$, $-NHC(O)R^9$, $-N(OH)CHO$, $-C(O)NHSO_2(1-4C)alkyl$, $-NHSO_2R^9$, $(R^9)(R^{10})NSO_2-$, $-COCH_2OR^{11}$, $-COCH_2OH$,

25 $(R^9)(R^{10})N-$, $-COOR^9$, $-CH_2OR^9$, $-CH_2COOR^9$ and $-CH_2OCOR^9$;

R^9 and R^{10} are independently selected from hydrogen, hydroxy and $(1-4C)alkyl$ optionally substituted by 1 or 2 R^{11});

R^{11} is $(1-4C)alkyl$.

30 In a further aspect of the invention, is provided a compound of the formula (I) or a pharmaceutically acceptable salt or pro-drug thereof, wherein

A is phenylene;

n is 0;

Z is nitrogen;

R^4 and R^5 are together $-S-C(R^6)=C(R^7)-$ or $-C(R^7)=C(R^6)-S-$;

R^6 and R^7 are independently selected from hydrogen and chloro;

Y is selected from $-C(O)R^2$, $-C(O)OR^2$, $-C(O)NR^2R^3$, $-(1-4C)alkyl$ [optionally substituted

5 by a substituent selected from hydroxy, (1-4C)alkoxy, aryloxy, heterocycloxy, $-S(O)_bR^2$ (wherein b is 0, 1 or 2), $-O-S(O)_bR^2$ (wherein b is 0, 1 or 2), $-NR^2R^3$, $-N(OH)R^2$, $-NR^2C(=O)R^2$, aryl and heterocyclyl], $-C(O)NOH$, $-(1-4C)alkylC(O)R^2$, $-(1-4C)alkylC(O)OR^2$, $-(1-4C)alkylOC(O)R^2$, $-(1-4C)alkylC(O)NR^2R^3$, $-(1-4C)alkylOC(O)OR^2$, $-(1-4C)alkylN(R^2)C(O)OR^2$, $-(1-4C)alkylN(R^2)C(O)NR^2R^3$,
10 and $-(1-4C)alkylOC(O)NR^2R^3$, aryl and heterocyclyl (wherein the heterocyclic ring is linked by a ring carbon atom);

R^2 and R^3 are independently selected from hydrogen, $-O(1-4C)alkyl$, $-N(1-4C)alkyl$, (1-4C)alkyl [optionally substituted by 1 or 2 R^8 groups]; or an NR^2R^3 group forms a morpholine, thiomorpholine (and oxidised versions thereof), pyrrolidine, or piperidine ring and wherein
15 the ring is optionally substituted by 1 or 2 substituents independently selected from chloro, fluoro, hydroxy and methoxy;

R^8 is independently selected from hydrogen, hydroxy, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkanoyl, $-COCOR^9$, $-C(O)N(R^9)(R^{10})$, $-NHC(O)R^9$, $-N(OH)CHO$, $-C(O)NHSO_2((1-4C)alkyl)$, $-NHSO_2R^9$, $(R^9)(R^{10})NSO_2-$, $-COCH_2OR^{11}$, $-COCH_2OH$,
20 $(R^9)(R^{10})N-$, $-COOR^9$, $-CH_2OR^9$, $-CH_2COOR^9$ and $-CH_2OCOR^9$;

R^9 and R^{10} are independently selected from hydrogen, hydroxy and (1-4C)alkyl optionally substituted by 1 or 2 R^{11});

R^{11} is (1-4C)alkyl.

25 In one aspect of the invention is provided a compound of the formula (I) or a pharmaceutically acceptable salt or pro-drug thereof, wherein

A is heteroarylene;

n is 0, 1 or 2;

R^1 is selected from fluoro, chloro, methyl, ethyl, methoxy and $-O-CH_2-O-$;

30 Z is nitrogen;

R^4 and R^5 are together $-S-C(R^6)=C(R^7)-$ or $-C(R^7)=C(R^6)-S-$;

R^6 and R^7 are independently selected from hydrogen, chloro, bromo or methyl;

- Y is selected from $-C(O)R^2$, $-C(O)OR^2$, $-C(O)NR^2R^3$, $-(1-4C)alkyl$ [optionally substituted by 1 or 2 substituents independently selected from hydroxy, $-C=NR^2$, $(1-4C)alkoxy$, aryloxy, heterocyclyloxy, $-S(O)_bR^2$ (wherein b is 0, 1 or 2), $-O-S(O)_bR^2$ (wherein b is 0, 1 or 2), $-NR^2R^3$, $-N(OH)R^2$, $-NR^2C(=O)R^2$, $-NHOHC(=O)R^2$, $-SO_2NR^2R^3$, $-N(R^2)SO_2R^2$, aryl and
- 5 heterocyclyl], $-C(O)NOH$, $-C(O)NSH$, $-C(N)OH$, $-SO_2H$, $-SO_3H$, $-SO_2NR^2R^3$, $-(1-4C)alkylC(O)R^2$, $-(1-4C)alkylC(O)OR^2$, $-(1-4C)alkylOC(O)R^2$, $-(1-4C)alkylC(O)NR^2R^3$, $-(1-4C)alkylOC(O)OR^2$, $-(1-4C)alkylN(R^2)C(O)OR^2$, $-(1-4C)alkylN(R^2)C(O)NR^2R^3$, and $-(1-4C)alkylOC(O)NR^2R^3$, $-S(O)_cR^2$ (wherein c is 0, 1 or 2), aryl and heterocyclyl (wherein the heterocyclic ring is linked by a ring carbon atom);
- 10 R^2 and R^3 are independently selected from hydrogen, $-O(1-4C)alkyl$, $-N(1-4C)alkyl$, $(1-4C)alkyl$ [optionally substituted by 1 or 2 R^8 groups]; or an NR^2R^3 group forms a 5 or 6 membered saturated, partially saturated or unsaturated ring, optionally containing 1, 2 or 3 additional heteroatoms independently selected from N, O and S, wherein any $-CH_2-$ may optionally be replaced by $-C(=O)-$, and any N or S atom may optionally be oxidised to form
- 15 an N-oxide or SO or SO_2 group respectively, and wherein the ring is optionally substituted by 1 or 2 substituents independently selected from halo, cyano, $(1-4C)alkyl$, hydroxy, $(1-4C)alkoxy$ and $(1-4C)alkylS(O)_b-$ (wherein b is 0, 1 or 2);
- R^8 is independently selected from hydrogen, hydroxy, $(1-4C)alkyl$, $(1-4C)alkoxy$, amino $(1-4C)alkyl$, halo $(1-4C)alkyl$, dihalo $(1-4C)alkyl$, trihalo $(1-4C)alkyl$,
- 20 hydroxy $(1-4C)alkyl$, dihydroxy $(1-4C)alkyl$, $(1-4C)alkoxy(1-4C)alkoxy$, $(1-4C)alkoxy(1-4C)alkyl$, hydroxy $(1-4C)alkoxy$, $(1-4C)alkanoyl$, $(1-4C)alkylS(O)_b-$ (wherein b is 0, 1 or 2), $(1-4C)alkylS(O)_c(1-4C)alkyl-$ (wherein c is 0, 1 or 2), $-N(OH)CHO$, $-COCOOR^9$, $-C(O)N(R^9)(R^{10})$, $-NHC(O)R^9$, $-C(O)NHSO_2(1-4C)alkyl$, $-NHSO_2R^9$, $(R^9)(R^{10})NSO_2-$, $-COCH_2OR^{11}$, $-COCH_2OH$, $(R^9)(R^{10})N-$, $-COOR^9$, $-CH_2OR^9$, $-CH_2COOR^9$ and $-$
- 25 CH_2OCOR^9 ;
- R^9 and R^{10} are independently selected from hydrogen, hydroxy and $(1-4C)alkyl$;
- R^{11} is $(1-4C)alkyl$.

In a further aspect of the invention, is provided a compound of the formula (I) or a

30 pharmaceutically acceptable salt or pro-drug thereof, wherein

A is heteroarylene;

n is 0, 1 or 2;

R^1 is selected from fluoro, chloro, methyl, ethyl, methoxy and $-O-CH_2-O-$;

Z is nitrogen;

R^4 and R^5 are together $-S-C(R^6)=C(R^7)-$ or $-C(R^7)=C(R^6)-S-$;

R^6 and R^7 are independently selected from hydrogen, chloro, bromo or methyl;

Y is selected from $-C(O)R^2$, $-C(O)OR^2$, $-C(O)NR^2R^3$, $-(1-4C)alkyl$ [optionally substituted

5 by a substituent selected from hydroxy, $(1-4C)alkoxy$, aryloxy, heterocyclyloxy, $-S(O)_bR^2$ (wherein b is 0, 1 or 2), $-O-S(O)_bR^2$ (wherein b is 0, 1 or 2), $-NR^2R^3$, $-N(OH)R^2$, $-NR^2C(=O)R^2$, aryl and heterocyclyl], $-C(O)NOH$, $-(1-4C)alkylC(O)R^2$, $-(1-4C)alkylC(O)OR^2$, $-(1-4C)alkylOC(O)R^2$, $-(1-4C)alkylC(O)NR^2R^3$, $-(1-4C)alkylOC(O)OR^2$, $-(1-4C)alkylN(R^2)C(O)OR^2$, $-(1-4C)alkylN(R^2)C(O)NR^2R^3$,
10 and $-(1-4C)alkylOC(O)NR^2R^3$, aryl and heterocyclyl (wherein the heterocyclic ring is linked by a ring carbon atom);

R^2 and R^3 are independently selected from hydrogen, $-O(1-4C)alkyl$, $-N(1-4C)alkyl$, $(1-4C)alkyl$ [optionally substituted by 1 or 2 R^8 groups]; or an NR^2R^3 group forms a morpholine, thiomorpholine (and oxidised versions thereof), pyrrolidine, dihydropyridine,

15 tetrahydropyridine, piperazine or piperidine ring and wherein the ring is optionally substituted by 1 or 2 substituents independently selected from halo, hydroxy and $(1-4C)alkoxy$;

R^8 is independently selected from hydrogen, hydroxy, $(1-4C)alkyl$, $(1-4C)alkoxy$, $(1-4C)alkanoyl$, $-COCOOR^9$, $-C(O)N(R^9)(R^{10})$, $-NHC(O)R^9$, $-N(OH)CHO$, $-C(O)NHSO_2((1-4C)alkyl)$, $-NHSO_2R^9$, $(R^9)(R^{10})NSO_2-$, $-COCH_2OR^{11}$, $-COCH_2OH$, $(R^9)(R^{10})N-$, $-COOR^9$,
20 $-CH_2OR^9$, $-CH_2COOR^9$ and $-CH_2OCOR^9$;

R^9 and R^{10} are independently selected from hydrogen, hydroxy and $(1-4C)alkyl$;

R^{11} is $(1-4C)alkyl$.

In a further aspect of the invention, is provided a compound of the formula (I) or a

25 pharmaceutically acceptable salt or pro-drug thereof, wherein

A is heteroarylene;

n is 0;

Z is nitrogen;

R^4 and R^5 are together $-S-C(R^6)=C(R^7)-$ or $-C(R^7)=C(R^6)-S-$;

30 R^6 and R^7 are independently selected from hydrogen and chloro;

Y is selected from $-C(O)R^2$, $-C(O)OR^2$, $-C(O)NR^2R^3$, $-(1-4C)alkyl$ [optionally substituted by a substituent selected from hydroxy, $(1-4C)alkoxy$, aryloxy, heterocyclyloxy, $-S(O)_bR^2$

(wherein b is 0, 1 or 2), $-O-S(O)_bR^2$ (wherein b is 0, 1 or 2), $-NR^2R^3$, $-N(OH)R^2$, $-NR^2C(=O)R^2$, aryl and heterocyclyl], $-C(O)NOH$, $-(1-4C)alkylC(O)R^2$, $-(1-4C)alkylC(O)OR^2$, $-(1-4C)alkylOC(O)R^2$, $-(1-4C)alkylC(O)NR^2R^3$, $-(1-4C)alkylOC(O)OR^2$, $-(1-4C)alkylN(R^2)C(O)OR^2$, $-(1-4C)alkylN(R^2)C(O)NR^2R^3$,
 5 and $-(1-4C)alkylOC(O)NR^2R^3$, aryl and heterocyclyl (wherein the heterocyclic ring is linked by a ring carbon atom);

R^2 and R^3 are independently selected from hydrogen, $-O(1-4C)alkyl$, $-N(1-4C)alkyl$, $(1-4C)alkyl$ [optionally substituted by 1 or 2 R^8 groups]; or an NR^2R^3 group forms a morpholine, thiomorpholine (and oxidised versions thereof), pyrrolidine, or piperidine ring and wherein
 10 the ring is optionally substituted by 1 or 2 substituents independently selected from chloro, fluoro, hydroxy and methoxy;

R^8 is independently selected from hydrogen, hydroxy, $(1-4C)alkyl$, $(1-4C)alkoxy$, $(1-4C)alkanoyl$, $-COCOOR^9$, $-C(O)N(R^9)(R^{10})$, $-NHC(O)R^9$, $-N(OH)CHO$, $-C(O)NHSO_2((1-4C)alkyl)$, $-NHSO_2R^9$, $(R^9)(R^{10})NSO_2-$, $-COCH_2OR^{11}$, $-COCH_2OH$,
 15 $(R^9)(R^{10})N-$, $-COOR^9$, $-CH_2OR^9$, $-CH_2COOR^9$ and $-CH_2OCOR^9$;

R^9 and R^{10} are independently selected from hydrogen, hydroxy and $(1-4C)alkyl$ optionally substituted by 1 or 2 R^{11} ;

R^{11} is $(1-4C)alkyl$.

In one aspect of the invention is provided a compound of the formula (I) or a
 20 pharmaceutically acceptable salt or pro-drug thereof, wherein

A is phenylene;

n is 0, 1 or 2;

Z is CH ;

R^4 and R^5 are together $-S-C(R^6)=C(R^7)-$ or $-C(R^7)=C(R^6)-S-$;

25 R^6 and R^7 are independently selected from hydrogen, chloro, bromo or methyl;

R^1 is selected from fluoro, chloro, methyl, ethyl, methoxy and $-O-CH_2-O-$;

Y is selected from $-C(O)R^2$, $-C(O)OR^2$, $-C(O)NR^2R^3$, $-(1-4C)alkyl$ [optionally substituted by 1 or 2 substituents independently selected from hydroxy, $-C=NR^2$, $(1-4C)alkoxy$, aryloxy, heterocyclyloxy, $-S(O)_bR^2$ (wherein b is 0, 1 or 2), $-O-S(O)_bR^2$ (wherein b is 0, 1 or 2),
 30 $-NR^2R^3$, $-N(OH)R^2$, $-NR^2C(=O)R^2$, $-NHOHC(=O)R^2$, $-SO_2NR^2R^3$, $-N(R^2)SO_2R^2$, aryl and heterocyclyl], $-C(O)NOH$, $-C(O)NSH$, $-C(N)OH$, $-SO_2H$, $-SO_3H$, $-SO_2NR^2R^3$, $-(1-4C)alkylC(O)R^2$, $-(1-4C)alkylC(O)OR^2$, $-(1-4C)alkylOC(O)R^2$,

-(1-4C)alkylC(O)NR²R³, -(1-4C)alkylOC(O)OR², -(1-4C)alkylN(R²)C(O)OR², -(1-4C)alkylN(R²)C(O)NR²R³, -(1-4C)alkylOC(O)NR²R³-S(O)_cR² (wherein c is 0, 1 or 2), -(1-4C)alkylSC(O)R², -(1-4C)alkylSO₂(2-4C)alkenyl, aryl and heterocyclyl (wherein the heterocyclic ring is linked by a ring carbon atom);

- 5 R² and R³ are independently selected from hydrogen, -O(1-4C)alkyl, -N(1-4C)alkyl, (1-4C)alkyl [optionally substituted by 1 or 2 R⁸ groups]; or an NR²R³ group forms a 5 or 6 membered saturated, partially saturated or unsaturated ring, optionally containing 1, 2 or 3 additional heteroatoms independently selected from N, O and S, wherein any -CH₂- may optionally be replaced by -C(=O)-, and any N or S atom may optionally be oxidised to form
 10 an N-oxide or SO or SO₂ group respectively, and wherein the ring is optionally substituted by 1 or 2 substituents independently selected from halo, cyano, (1-4C)alkyl, hydroxy, (1-4C)alkoxy and (1-4C)alkylS(O)_b- (wherein b is 0, 1 or 2);

R⁸ is independently selected from hydrogen, hydroxy, (1-4C)alkyl,

- (1-4C)alkoxy, amino(1-4C)alkyl, halo(1-4C)alkyl, dihalo(1-4C)alkyl, trihalo(1-4C)alkyl,
 15 hydroxy(1-4C)alkyl, dihydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkoxy, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkoxy, (1-4C)alkanoyl, (1-4C)alkylS(O)_b- (wherein b is 0, 1 or 2, (1-4C)alkylS(O)_c(1-4C)alkyl- (wherein c is 0, 1 or 2), -N(OH)CHO, -COCOOR⁹, -C(O)N(R⁹)(R¹⁰), -NHC(O)R⁹, -C(O)NHSO₂((1-4C)alkyl), -NHSO₂R⁹, (R⁹)(R¹⁰)NSO₂-, -COCH₂OR¹¹, -COCH₂OH, (R⁹)(R¹⁰)N-, -COOR⁹, -CH₂OR⁹, -CH₂COOR⁹ and -
 20 CH₂OCOR⁹;

R⁹ and R¹⁰ are independently selected from hydrogen, hydroxy and (1-4C)alkyl optionally substituted by 1 or 2 R¹¹;

R¹¹ is (1-4C)alkyl.

- 25 In a further aspect of the invention, is provided a compound of the formula (I) or a pharmaceutically acceptable salt or pro-drug thereof, wherein

A is phenylene;

n is 0, 1 or 2;

R¹ is selected from fluoro, chloro, methyl, ethyl, methoxy and -O-CH₂-O-;

- 30 Z is CH;

R⁴ and R⁵ are together -S-C(R⁶)=C(R⁷)- or -C(R⁷)=C(R⁶)-S-;

R⁶ and R⁷ are independently selected from hydrogen, chloro, bromo or methyl;

- Y is selected from $-C(O)R^2$, $-C(O)OR^2$, $-C(O)NR^2R^3$, $-(1-4C)alkyl$ [optionally substituted by a substituent selected from hydroxy, $(1-4C)alkoxy$, aryloxy, heterocycloxy, $-S(O)_bR^2$ (wherein b is 0, 1 or 2), $-O-S(O)_bR^2$ (wherein b is 0, 1 or 2), $-NR^2R^3$, $-N(OH)R^2$, $-NR^2C(=O)R^2$, aryl and heterocyclyl], $-C(O)NOH$, $-(1-4C)alkylC(O)R^2$,
 5 $-(1-4C)alkylC(O)OR^2$, $-(1-4C)alkylOC(O)R^2$, $-(1-4C)alkylC(O)NR^2R^3$,
 $-(1-4C)alkylOC(O)OR^2$, $-(1-4C)alkylN(R^2)C(O)OR^2$, $-(1-4C)alkylN(R^2)C(O)NR^2R^3$,
 $-(1-4C)alkylOC(O)NR^2R^3$, $-(1-4C)alkylSC(O)R^2$, $-(1-4C)alkylSO_2(2-4C)alkenyl$,
 aryl and heterocyclyl (wherein the heterocyclic ring is linked by a ring carbon atom);
 R^2 and R^3 are independently selected from hydrogen, $-O(1-4C)alkyl$, $-N(1-4C)alkyl$, $(1-4C)alkyl$ [optionally substituted by 1 or 2 R^8 groups]; or an NR^2R^3 group forms a morpholine,
 10 thiomorpholine (and oxidised versions thereof), pyrrolidine, dihydropyridine,
 tetrahydropyridine, piperazine or piperidine ring and wherein the ring is optionally substituted by 1 or 2 substituents independently selected from halo, hydroxy and $(1-4C)alkoxy$;
 R^8 is independently selected from hydrogen, hydroxy, $(1-4C)alkyl$,
 15 $(1-4C)alkoxy$, $(1-4C)alkanoyl$, $-COCOOR^9$, $-C(O)N(R^9)(R^{10})$, $-NHC(O)R^9$, $-N(OH)CHO$,
 $-C(O)NHOSO_2(1-4C)alkyl$, $-NHOSO_2R^9$, $(R^9)(R^{10})NSO_2$, $-COCH_2OR^{11}$, $-COCH_2OH$,
 $(R^9)(R^{10})N$, $-COOR^9$, $-CH_2OR^9$, $-CH_2COOR^9$ and $-CH_2OCOR^9$;
 R^9 and R^{10} are independently selected from hydrogen, hydroxy and $(1-4C)alkyl$ optionally substituted by 1 or 2 R^{11});
 20 R^{11} $(1-4C)alkyl$.

In a further aspect of the invention, is provided a compound of the formula (I) or a pharmaceutically acceptable salt or pro-drug thereof, wherein

A is phenylene;

25 n is 0;

Z is CH;

R^4 and R^5 are together $-S-C(R^6)=C(R^7)-$ or $-C(R^7)=C(R^6)-S-$;

R^6 and R^7 are independently selected from hydrogen and chloro;

- Y is selected from $-C(O)R^2$, $-C(O)OR^2$, $-C(O)NR^2R^3$, $-(1-4C)alkyl$ [optionally substituted
 30 by a substituent selected from hydroxy, $(1-4C)alkoxy$, aryloxy, heterocycloxy, $-S(O)_bR^2$ (wherein b is 0, 1 or 2), $-O-S(O)_bR^2$ (wherein b is 0, 1 or 2), $-NR^2R^3$, $-N(OH)R^2$,
 $-NR^2C(=O)R^2$, aryl and heterocyclyl], $-C(O)NOH$, $-(1-4C)alkylC(O)R^2$,
 $-(1-4C)alkylC(O)OR^2$, $-(1-4C)alkylOC(O)R^2$, $-(1-4C)alkylC(O)NR^2R^3$,

-(1-4C)alkylOC(O)OR², -(1-4C)alkylN(R²)C(O)OR², -(1-4C)alkylN(R²)C(O)NR²R³,
 -(1-4C)alkylSC(O)R², -(1-4C)alkylOC(O)NR²R³, -(1-4C)alkylSO₂(2-4C)alkenyl, aryl and
 heterocyclyl (wherein the heterocyclic ring is linked by a ring carbon atom);

R² and R³ are independently selected from hydrogen, -O(1-4C)alkyl, -N(1-4C)alkyl, (1-

5 4C)alkyl [optionally substituted by 1 or 2 R⁸ groups]; or an NR²R³ group forms a morpholine,
 thiomorpholine (and oxidised versions thereof), pyrrolidine, or piperidine ring and wherein
 the ring is optionally substituted by 1 or 2 substituents independently selected from chloro,
 fluoro, hydroxy and methoxy;

R⁸ is independently selected from hydrogen, hydroxy, (1-4C)alkyl,

10 (1-4C)alkoxy, (1-4C)alkanoyl, -COCOOR⁹, -C(O)N(R⁹)(R¹⁰), -NHC(O)R⁹, -N(OH)CHO,
 -C(O)NHOSO₂(1-4C)alkyl, -NHOSO₂R⁹, (R⁹)(R¹⁰)NSO₂-, -COCH₂OR¹¹, -COCH₂OH,
 (R⁹)(R¹⁰)N-, -COOR⁹, -CH₂OR⁹, -CH₂COOR⁹ and -CH₂OCOR⁹;

R⁹ and R¹⁰ are independently selected from hydrogen, hydroxy and (1-4C)alkyl optionally
 substituted by 1 or 2 R¹¹;

15 R¹¹ is (1-4C)alkyl.

In a further aspect of the invention, is provided a compound of the formula (I) or a
 pharmaceutically acceptable salt or pro-drug thereof, wherein

A is phenylene;

20 n is 0;

Z is CH;

R⁴ and R⁵ are together -S-C(R⁶)=C(R⁷)- or -C(R⁷)=C(R⁶)-S-;

R⁶ and R⁷ are independently selected from hydrogen and chloro;

Y is selected from -C(O)R², -C(O)OR², -C(O)NR²R³, -(1-4C)alkyl [optionally substituted
 25 by a substituent selected from hydroxy, (1-4C)alkoxy, aryloxy, heterocycloxy, -S(O)_bR²
 (wherein b is 0, 1 or 2), -O-S(O)_bR² (wherein b is 0, 1 or 2), -NR²R³, -N(OH)R²,

-NR²C(=O)R², -SO₂NR²R³, aryl and heterocyclyl], -C(O)NOH, -(1-4C)alkylC(O)R²,
 -(1-4C)alkylC(O)OR², -(1-4C)alkylOC(O)R², -(1-4C)alkylC(O)NR²R³,

30 -(1-4C)alkylOC(O)OR², -(1-4C)alkylN(R²)C(O)OR², -(1-4C)alkylN(R²)C(O)NR²R³, -(1-
 4C)alkylSC(O)R², -(1-4C)alkylOC(O)NR²R³, -(1-4C)alkylSO₂(2-4C)alkenyl, -SO_cR²
 (wherein c is 0, 1 or 2), aryl and heterocyclyl (wherein the heterocyclic ring is linked by a ring
 carbon atom);

R^2 and R^3 are independently selected from hydrogen, heterocyclyl, -O(1-4C)alkyl, -N(1-4C)alkyl, (1-4C)alkyl [optionally substituted by 1 or 2 R^8 groups]; or an NR^2R^3 group forms a morpholine, thiomorpholine (and oxidised versions thereof), pyrrolidine, or piperidine ring and wherein the ring is optionally substituted by 1 or 2 substituents independently selected

5 from chloro, fluoro, hydroxy and methoxy;

R^8 is independently selected from hydrogen, hydroxy, (1-4C)alkyl,

(1-4C)alkoxy, (1-4C)alkanoyl, -COCOOR⁹, -C(O)N(R⁹)(R¹⁰), -NHC(O)R⁹, -N(OH)CHO,

-C(O)NHSO₂(1-4C)alkyl, -NHSO₂R⁹, (R⁹)(R¹⁰)NSO₂-, -COCH₂OR¹¹, -COCH₂OH,

(R⁹)(R¹⁰)N-, -COOR⁹, -CH₂OR⁹, -CH₂COOR⁹, -CH₂OCOR⁹, aryl, heterocyclyl, and 5- and

10 6-membered cyclic acetals and mono- and di-methyl derivatives thereof;

R^9 and R^{10} are independently selected from hydrogen, hydroxy and (1-4C)alkyl optionally substituted by 1 or 2 R^{11}); or

R^9 and R^{10} together with the nitrogen to which they are attached form a 4- to 6-membered ring as hereinbefore defined;

15 R^{11} is (1-4C)alkyl.

In a further aspect of the invention, is provided a compound of the formula (I) or a pharmaceutically acceptable salt or pro-drug thereof, wherein

A is phenylene;

20 n is 0;

Z is CH;

R^4 and R^5 are together -S-C(R⁶)=C(R⁷)- or -C(R⁷)=C(R⁶)-S-;

R^6 and R^7 are independently selected from hydrogen and chloro;

Y is selected from -C(O)OR², -C(O)NR²R³, -(1-4C)alkyl [optionally substituted by a

25 substituent selected from hydroxy, (1-4C)alkoxy, -S(O)_bR² (wherein b is 0, 1 or 2), -O-

S(O)_bR² (wherein b is 0, 1 or 2), -NR²R³, -NR²C(=O)R² and -SO₂NR²R³],

-(1-4C)alkylC(O)R², -(1-4C)alkylC(O)OR², -(1-4C)alkylOC(O)R², -(1-4C)alkylC(O)NR²R³,

-(1-4C)alkylOC(O)OR², -(1-4C)alkylN(R²)C(O)OR², -(1-4C)alkylN(R²)C(O)NR²R³, -(1-

4C)alkylSC(O)R², -(1-4C)alkylOC(O)NR²R³, -(1-4C)alkylSO₂(2-4C)alkenyl, -SO_cR²

30 (wherein c is 0, 1 or 2);

R^2 and R^3 are independently selected from hydrogen, heterocyclyl, -O(1-4C)alkyl, -N(1-4C)alkyl, (1-4C)alkyl [optionally substituted by 1 or 2 R^8 groups]; or an NR^2R^3 group forms a morpholine, thiomorpholine (and oxidised versions thereof), pyrrolidine, or piperidine ring

and wherein the ring is optionally substituted by 1 or 2 substituents independently selected from chloro, fluoro, hydroxy and methoxy;

R^8 is independently selected from hydrogen, hydroxy, $-C(O)N(R^9)(R^{10})$, $-NHC(O)R^9$, $-COOR^9$, $-CH_2OR^9$, $-CH_2COOR^9$, $-CH_2OCOR^9$, aryl, heterocyclyl, and 5- and 6-membered cyclic acetals and mono- and di-methyl derivatives thereof;

R^9 and R^{10} are independently selected from hydrogen, hydroxy and (1-4C)alkyl; or R^9 and R^{10} together with the nitrogen to which they are attached form a 4- to 6-membered ring as hereinbefore defined.

10 In a further aspect of the invention, is provided a compound of the formula (I) or a pharmaceutically acceptable salt or pro-drug thereof, wherein

A is phenylene;

n is 0;

Z is CH;

15 R^4 and R^5 are together $-S-C(R^6)=C(R^7)-$ or $-C(R^7)=C(R^6)-S-$;

R^6 and R^7 are independently selected from hydrogen and chloro;

Y is selected from $-C(O)OR^2$, $-C(O)NR^2R^3$, $-(1-4C)alkyl$ [optionally substituted by a substituent selected from hydroxy, (1-4C)alkoxy, $-S(O)_bR^2$ (wherein b is 0, 1 or 2), $-O-S(O)_bR^2$ (wherein b is 0, 1 or 2), $-NR^2R^3$, $-NR^2C(=O)R^2$ and $-SO_2NR^2R^3$],

20 $-(1-4C)alkylC(O)R^2$, $-(1-4C)alkylC(O)OR^2$, $-(1-4C)alkylOC(O)R^2$, $-(1-4C)alkylC(O)NR^2R^3$, $-(1-4C)alkylOC(O)OR^2$, $-(1-4C)alkylN(R^2)C(O)OR^2$, $-(1-4C)alkylN(R^2)C(O)NR^2R^3$, $-(1-4C)alkylSC(O)R^2$, $-(1-4C)alkylOC(O)NR^2R^3$, $-(1-4C)alkylSO_2(2-4C)alkenyl$, $-SO_cR^2$ (wherein c is 0, 1 or 2);

R^2 and R^3 are independently selected from hydrogen, heterocyclyl, $-O(1-4C)alkyl$, $-N(1-$

25 $4C)alkyl$, (1-4C)alkyl [optionally substituted by 1 or 2 R^8 groups]; or an NR^2R^3 group forms a morpholine, thiomorpholine (and oxidised versions thereof), pyrrolidine, or piperidine ring and wherein the ring is optionally substituted by 1 or 2 substituents independently selected from chloro, fluoro, hydroxy and methoxy;

R^8 is independently selected from hydrogen, hydroxy, $-C(O)N(R^9)(R^{10})$, $-NHC(O)R^9$,

30 $-COOR^9$, $-CH_2OR^9$, $-CH_2COOR^9$, $-CH_2OCOR^9$, aryl, heterocyclyl, and 5- and 6-membered cyclic acetals and mono- and di-methyl derivatives thereof;

R^9 and R^{10} are independently selected from hydrogen, hydroxy and (1-4C)alkyl; or R^9 and R^{10} together with the nitrogen to which they are attached form a morpholine, thiomorpholine (and oxidised versions thereof), pyrrolidine, or piperidine ring.

- 5 In a further aspect of the invention, is provided a compound of the formula (I) or a pharmaceutically acceptable salt or pro-drug thereof, wherein
- A is phenylene;
- n is 0;
- Z is CH;
- 10 R^4 and R^5 are together $-S-C(R^6)=C(R^7)-$ or $-C(R^7)=C(R^6)-S-$;
- R^6 and R^7 are independently selected from hydrogen and chloro;
- Y is selected from $-C(O)OR^2$, $-C(O)NR^2R^3$, $-(1-4C)alkyl$ [optionally substituted by a substituent selected from $-S(O)_bR^2$ (wherein b is 0, 1 or 2), $-O-S(O)_bR^2$ (wherein b is 0, 1 or 2), $-NR^2R^3$, $-NR^2C(=O)R^2$ and $-SO_2NR^2R^3$], $-(1-4C)alkylC(O)OR^2$, $-(1-4C)alkylOC(O)R^2$,
- 15 $-(1-4C)alkylC(O)NR^2R^3$, $-(1-4C)alkylSC(O)R^2$, $-(1-4C)alkylSO_2(2-4C)alkenyl$ and $-SO_cR^2$ (wherein c is 0, 1 or 2);
- R^2 and R^3 are independently selected from hydrogen, heterocyclyl, and (1-4C)alkyl [optionally substituted by 1 or 2 R^8 groups]; or an NR^2R^3 group forms a morpholine, thiomorpholine (and oxidised versions thereof), pyrrolidine, or piperidine ring and wherein the ring is optionally
- 20 substituted by 1 or 2 substituents independently selected from chloro, fluoro, hydroxy and methoxy;
- R^8 is independently selected from hydrogen, hydroxy, $-C(O)N(R^9)(R^{10})$, $-NHC(O)R^9$, $-COOR^9$, aryl, heterocyclyl, and 5- and 6-membered cyclic acetals and mono- and di-methyl derivatives thereof;
- 25 R^9 and R^{10} are independently selected from hydrogen, hydroxy and (1-4C)alkyl; or R^9 and R^{10} together with the nitrogen to which they are attached form a morpholine ring.

In a further aspect of the invention, is provided a compound of the formula (I) or a pharmaceutically acceptable salt or pro-drug thereof, wherein

- 30 A is heteroarylene;
- n is 0, 1 or 2;
- R^1 is selected from fluoro, chloro, methyl, ethyl, methoxy and $-O-CH_2-O-$;
- Z is CH;

R^4 and R^5 are together $-S-C(R^6)=C(R^7)-$ or $-C(R^7)=C(R^6)-S-$;

R^6 and R^7 are independently selected from hydrogen, chloro, bromo or methyl;

Y is selected from $-C(O)R^2$, $-C(O)OR^2$, $-C(O)NR^2R^3$, $-(1-4C)alkyl$ [optionally substituted by a substituent selected from hydroxy, $(1-4C)alkoxy$, aryloxy, heterocycloxy, $-S(O)_bR^2$

5 (wherein b is 0, 1 or 2), $-O-S(O)_bR^2$ (wherein b is 0, 1 or 2), $-NR^2R^3$, $-N(OH)R^2$, $-NR^2C(=O)R^2$, aryl and heterocyclyl], $-C(O)NOH$, $-(1-4C)alkylC(O)R^2$, $-(1-4C)alkylC(O)OR^2$, $-(1-4C)alkylOC(O)R^2$, $-(1-4C)alkylC(O)NR^2R^3$, $-(1-4C)alkylOC(O)OR^2$, $-(1-4C)alkylN(R^2)C(O)OR^2$, $-(1-4C)alkylN(R^2)C(O)NR^2R^3$, $-(1-4C)alkylOC(O)NR^2R^3$, $-(1-4C)alkylSC(O)R^2$, $-(1-4C)alkylSO_2(2-4C)alkenyl$,

10 aryl and heterocyclyl (wherein the heterocyclic ring is linked by a ring carbon atom);

R^2 and R^3 are independently selected from hydrogen, $-O(1-4C)alkyl$, $-N(1-4C)alkyl$, $(1-4C)alkyl$ [optionally substituted by 1 or 2 R^8 groups]; or an NR^2R^3 group forms a morpholine, thiomorpholine (and oxidised versions thereof), pyrrolidine, dihydropyridine,

tetrahydropyridine, piperazine or piperidine ring and wherein the ring is optionally substituted

15 by 1 or 2 substituents independently selected from halo, hydroxy and $(1-4C)alkoxy$;

R^8 is independently selected from hydrogen, hydroxy, $(1-4C)alkyl$, $(1-4C)alkoxy$, $(1-4C)alkanoyl$, $-COCOOR^9$, $-C(O)N(R^9)(R^{10})$, $-NHC(O)R^9$, $-N(OH)CHO$, $-C(O)NHSO_2(1-4C)alkyl$, $-NHSO_2R^9$, $(R^9)(R^{10})NSO_2-$, $-COCH_2OR^{11}$, $-COCH_2OH$, $(R^9)(R^{10})N-$, $-COOR^9$, $-CH_2OR^9$, $-CH_2COOR^9$ and $-CH_2OCOR^9$;

20 R^9 and R^{10} are independently selected from hydrogen, hydroxy and $(1-4C)alkyl$;

R^{11} is $(1-4C)alkyl$.

In a further aspect of the invention, is provided a compound of the formula (I) or a pharmaceutically acceptable salt or pro-drug thereof, wherein

25 A is heteroarylene;

n is 0;

Z is CH;

R^4 and R^5 are together $-S-C(R^6)=C(R^7)-$ or $-C(R^7)=C(R^6)-S-$;

R^6 and R^7 are independently selected from hydrogen and chloro;

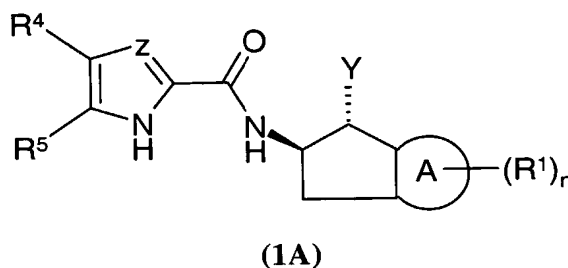
30 Y is selected from $-C(O)R^2$, $-C(O)OR^2$, $-C(O)NR^2R^3$, $-(1-4C)alkyl$ [optionally substituted by a substituent selected from hydroxy, $(1-4C)alkoxy$, aryloxy, heterocycloxy, $-S(O)_bR^2$ (wherein b is 0, 1 or 2), $-O-S(O)_bR^2$ (wherein b is 0, 1 or 2), $-NR^2R^3$, $-N(OH)R^2$, $-NR^2C(=O)R^2$, aryl and heterocyclyl], $-C(O)NOH$, $-(1-4C)alkylC(O)R^2$,

$-(1-4C)alkylC(O)OR^2$, $-(1-4C)alkylOC(O)R^2$, $-(1-4C)alkylC(O)NR^2R^3$,
 $-(1-4C)alkylOC(O)OR^2$, $-(1-4C)alkylN(R^2)C(O)OR^2$, $-(1-4C)alkylN(R^2)C(O)NR^2R^3$,
 $-(1-4C)alkylOC(O)NR^2R^3$, $-(1-4C)alkylSC(O)R^2$, $-(1-4C)alkylSO_2(2-4C)alkenyl$,
 aryl and heterocyclyl (wherein the heterocyclic ring is linked by a ring carbon atom);

- 5 R^2 and R^3 are independently selected from hydrogen, $-O(1-4C)alkyl$, $-N(1-4C)alkyl$, $(1-4C)alkyl$ [optionally substituted by 1 or 2 R^8 groups]; or an NR^2R^3 group forms a morpholine, thiomorpholine (and oxidised versions thereof), pyrrolidine, or piperidine ring and wherein the ring is optionally substituted by 1 or 2 substituents independently selected from chloro, fluoro, hydroxy and methoxy;
- 10 R^8 is independently selected from hydrogen, hydroxy, $(1-4C)alkyl$, $(1-4C)alkoxy$, $(1-4C)alkanoyl$, $-COCOOR^9$, $-C(O)N(R^9)(R^{10})$, $-NHC(O)R^9$, $-N(OH)CHO$, $-C(O)NHSO_2(1-4C)alkyl$, $-NHSO_2R^9$, $(R^9)(R^{10})NSO_2-$, $-COCH_2OR^{11}$, $-COCH_2OH$, $(R^9)(R^{10})N-$, $-COOR^9$, $-CH_2OR^9$, $-CH_2COOR^9$ and $-CH_2OCOR^9$; R^9 and R^{10} are independently selected from hydrogen, hydroxy and $(1-4C)alkyl$ optionally substituted by 1 or 2 R^{11} ;
- 15 R^{11} is $(1-4C)alkyl$.

Particular compounds of the invention are each of the Examples or a pharmaceutically-acceptable salt or pro-drug thereof, each of which provides a further independent aspect of the invention. In a further aspect of the invention there is provided any two or more of the Examples or a pharmaceutically-acceptable salt or pro-drug thereof.

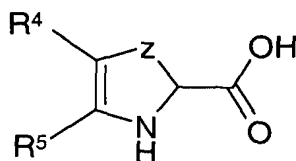
Preferred compounds of the invention are of the formula (1A), wherein Y, R^1 to R^7 and n are as defined in any aspect or embodiment described hereinbefore or hereinafter.



Another aspect of the present invention provides a process for preparing a compound of formula (1) or a pharmaceutically acceptable salt or an in-vivo hydrolysable ester thereof

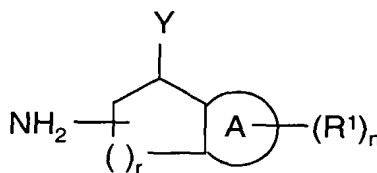
which process (wherein A, Y, R¹, R⁴, R⁵, r and n are, unless otherwise specified, as defined in formula (1)) comprises of:

a) reacting an acid of the formula (2):



(2)

or an activated derivative thereof; with an amine of formula (3):



(3)

and thereafter if necessary:

- i) converting a compound of the formula (1) into another compound of the formula (1);
- ii) removing any protecting groups;
- iii) forming a pharmaceutically acceptable salt or in-vivo hydrolysable ester.

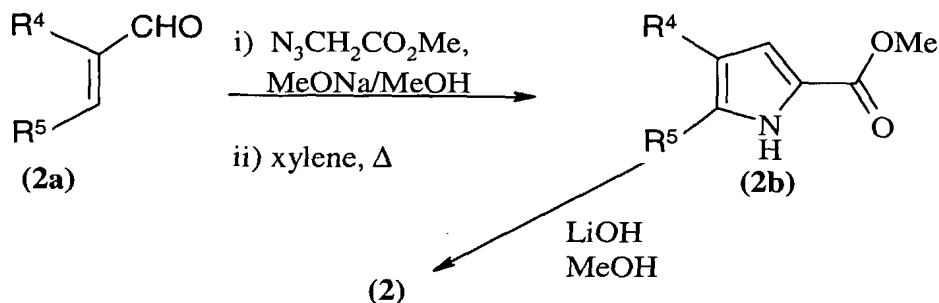
Specific reaction conditions for the above reaction are as follows.

Process a) Acids of formula (2) and amines of formula (3) may be coupled together in the presence of a suitable coupling reagent. Standard peptide coupling reagents known in the art can be employed as suitable coupling reagents, or for example carbonyldiimidazole, 1-ethyl-3-(3-dimethylaminopropyl)carbodi-imide hydrochloride (EDCI) and dicyclohexyl-carbodiimide (DCCI), optionally in the presence of a catalyst such as 1-hydroxybenzotriazole, dimethylaminopyridine or 4-pyrrolidinopyridine, optionally in the presence of a base for example triethylamine, di-isopropylethylamine, pyridine, or 2,6-di-*alkyl*-pyridines such as 2,6-lutidine or 2,6-di-*tert*-butylpyridine. Suitable solvents include dimethylacetamide, dichloromethane, benzene, tetrahydrofuran and dimethylformamide. The coupling reaction may conveniently be performed at a temperature in the range of -40 to 40°C.

Suitable activated acid derivatives include acid halides, for example acid chlorides, and active esters, for example pentafluorophenyl esters. The reaction of these types of compounds with amines is well known in the art, for example they may be reacted in the

presence of a base, such as those described above, and in a suitable solvent, such as those described above. The reaction may conveniently be performed at a temperature in the range of -40 to 40°C.

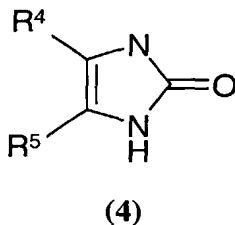
A compounds of formula (2) where Z is CH may be prepared according to Scheme 1:



Scheme 1

Compounds of formula (2a) are commercially available or they are known compounds or they are prepared by processes known in the art.

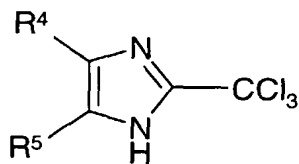
A compound of the formula (2) wherein X is nitrogen, can be prepared from a compound of the formula (4):



by firstly converting the oxo group to chlorine or bromine with a halogenating agent such as POCl₃ or POBr₃, in an inert organic solvent such as dichloromethane in a temperature range of ambient temperature to reflux (for example see *Nucleic Acid Chem.* 1991, 4, 24-6), then displacing the chlorine or bromine group with cyanide using a cyanide salt such as potassium cyanide, in an inert organic solvent such as toluene, benzene or xylene, optionally in the presence of a catalyst such as 18-crown-6 (for example see *J. Heterocycl. Chem* 2000, 37(1), 119-126) and finally hydrolysing the cyano group to a carboxy group, with for example, an aqueous acid such as aqueous hydrogen chloride (for example see *Chem. Pharm. Bull.* 1986, 34(9), 3635-43).

Alternatively, a compound of the formula (2) wherein X is nitrogen may be formed by reacting the compound of the formula (4) with (Cl₃CCO)₂O and Cl₃CCO₂H in the presence of magnesium chloride using Cl₃CCO₂H as solvent, to form a compound of the formula (5):

- 39 -

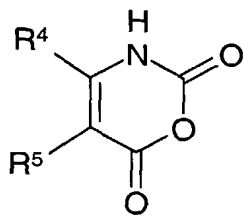


(5)

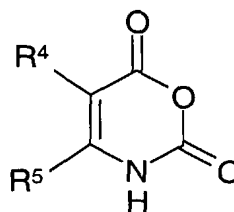
and then hydrolysing the compound of the formula (5), using, for example, aqueous sodium hydroxide, at a temperature range of ambient temperature to reflux (for example see *J*

5 *Heterocycl. Chem.* 1980, 17(2), 381-2).

The compound of formula (4) may be prepared from a compound of formula (6) and (7) using conditions known for the Curtius rearrangement (*Tetrahedron* 1999, 55, 6167):

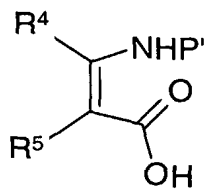


(6)

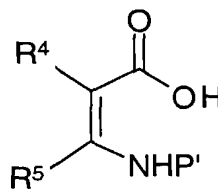


(7)

10 The compounds of the formula (8) and (9):



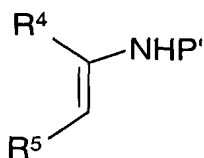
(8)



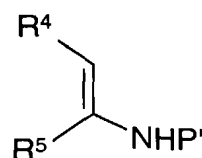
(9)

transform into compounds of the formula (6) and (7) respectively. This transformation either occurs spontaneously or may be induced with acid or base.

15 Compounds of the formula (8) and (9) may be prepared by introducing a carboxy group into a compound of the formula (10) or (11):



(10)



(11)

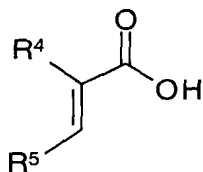
wherein P' is an amino protecting group such as butoxycarbonyl.

20 A carboxy group is introduced into the compound of the formula (10) or (11) by reacting an alkyl lithium reagent such as n-butyl lithium, in an inert organic solvent such as

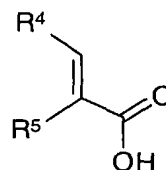
THF, at low temperature, for example in the range -10°C to -78°C and then forming the compound of the formula (8) or (9) as appropriate by either

- a) reacting the resulting compound with carbon dioxide; or
- b) by reacting with DMF in the temperature range of -10°C to ambient temperature to form the corresponding aldehyde and oxidizing the aldehyde to carboxy with standard reagents to give the compound of the formula (8) or (9).

Compounds of the formula (10) and (11) may be prepared from a compound of the formula (12) and (13):



(12)

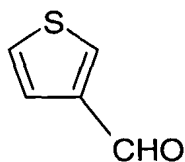


(13)

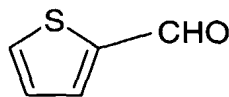
using conditions known for the Curtius reaction.

Compounds of the formula (12) and (13) may be prepared by oxidizing the corresponding aldehyde using standard oxidizing reagents such as potassium manganate or sodium periodate.

The aldehyde precursor of a compound of the formula (12) or (13) can be prepared using standard techniques known in the art. For example, many compounds of the formula (12) or (13) may be prepared by introducing the appropriate R^6 and R^7 into a compound of the formula (14) or (15) as appropriate:



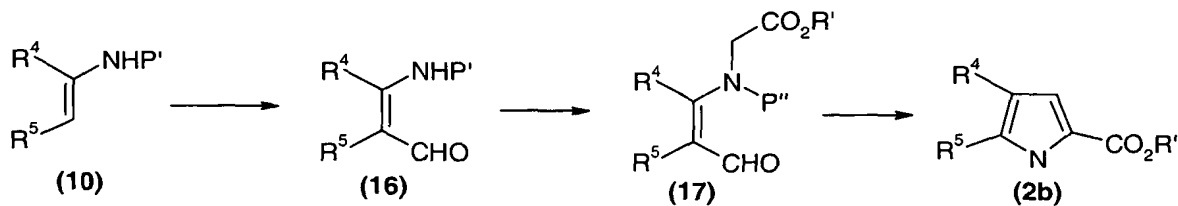
(14)



(15)

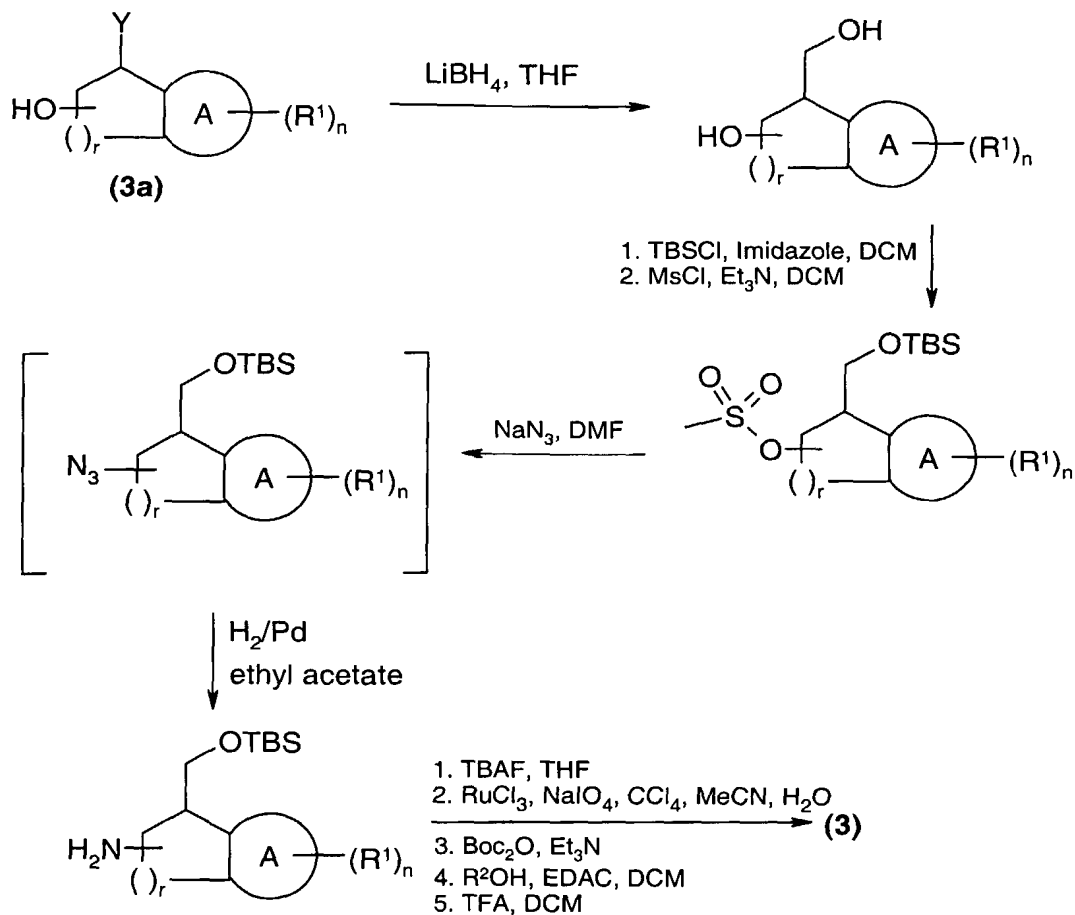
For example, when R^6 and R^7 are both chloro a compound of the formula (14) or (15) may be chlorinated with a chlorinating agent such as chlorine in the presence of aluminium chloride or iron (III) chloride, in an inert organic chlorinated solvent such as dichloromethane or 1,2-dichloroethane, followed by treatment with an aqueous base, such as, aqueous sodium hydroxide. The mono chlorinated compound can be formed in the same way.

Compounds of formula (2b) may also be prepared as illustrated in Scheme 2:

**Scheme 2**

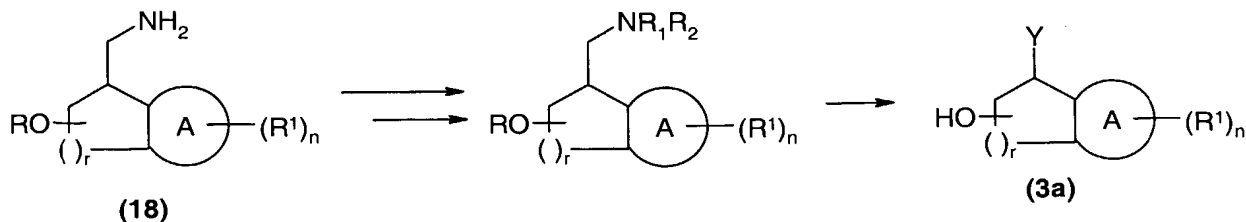
The conversion of compounds of formula (10) into compounds of formula (16) may be carried out by directed ortho lithiation reactions (J. Org. Chem, 2001, volume 66, 3662-3670), for example with n-butyl lithium and $(CHO)N(alkyl)_2$. The protecting group P' in compounds of formula (10) must be suitable directing group for this reaction and may be for example $-CO_2tBu$. Reaction of compounds of formula (16) with LCH_2CO_2R where L is a leaving group, and replacement of the protecting group P' with an alternative P'' (for example $-COalkyl$) according to standard processes, gives a compound of formula (17). This may be cyclised using a base, for example potassium carbonate or sodium methoxide.

Compounds of formula (3) where Y is $-C(O)R^2$ are known compounds or they are prepared by processes known in the art. When Y is $-C(O)OR^2$, the amines of formula (3) may be prepared according to Scheme 3:

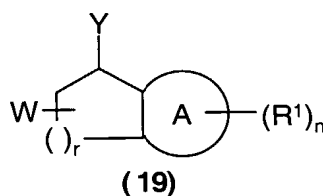


Scheme 3

Compounds of formula (3a) are commercially available or they are known compounds or they are prepared by processes known in the art. For example, starting from primary amines of formula (18), in which R is H or a suitable protecting group, one or both of R^1 and/or R^2 may be introduced by acylation, (for example reacting with acetoxyacetic acid and 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (EDAC)), alkylation, reductive alkylation, sulphonation or related processes, followed by O-deprotection when appropriate. Alternatively, one or both of R^1 and R^2 may be obtained by modification of functionality in groups previously thus introduced, by reduction, oxidation, hydrolysis (for example the conversion of an acetoxy group to a hydroxy group), nucleophilic displacement, amidation, or a related process, or a combination of these processes, followed by O-deprotection when appropriate. It will be appreciated that such modifications may include modifications which convert one compound of the formula (1) into another compound of the formula (1).



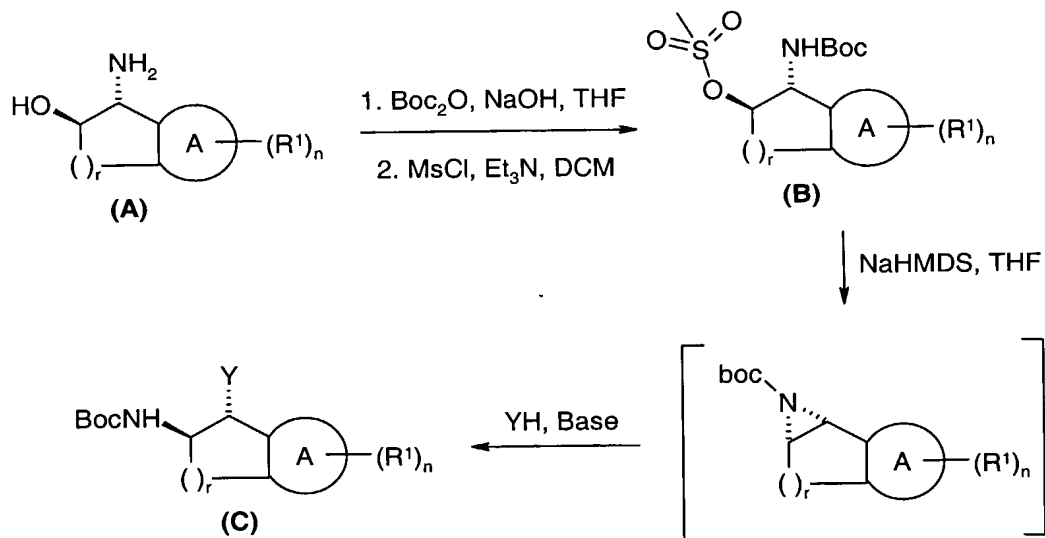
Amines of formula (3) may alternatively be obtained by applying the processes described for the preparation of compounds of formula (3a) to compounds of formula (19) in which W is NH₂ or a nitrogen atom with one or two suitable protecting groups.



5

Compounds of the formula (3) may be made by deprotection of compounds of formula (C), which are commercially available, known compounds, prepared by processes known in the art or may be prepared by the novel route shown in **Scheme 3A**, wherein Y is -SR, or -CH(CO₂R')₂, (wherein R represents R² as defined hereinbefore, or a group which may be converted to a group R² using standard chemistry; and wherein R' is (1-6C)alkyl).

10



Scheme 3A

Compound A (where r = 1; A = phenyl; R¹ = H) is commercially available [(1R,2R)-(-)-trans-1-Amino-2-indanol, Cas. Reg. No.:163061-73-2 or [(1S,2S)-(-)-trans-1-Amino-2-indanol Cas. Reg. No.:13286-59-4]. Compounds of type B can be prepared by methods known in the literature, such as those shown above in Scheme 3A. The conversion of

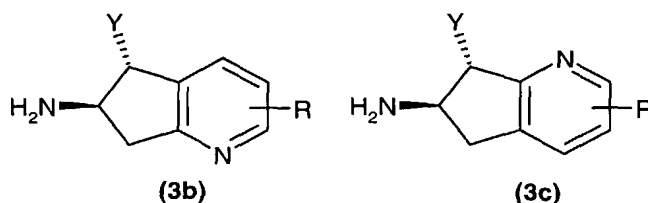
15

compounds of type B to C is novel and forms a further independent aspect of the invention. It will be appreciated that the process shown in Scheme 3A applies equally to the opposite enantiomers of compounds A, B and C to those shown. In compound (C), where Y = -CH(CO₂R')₂, the malonate ester can be transformed to a variety of functional groups by standard methods known in the art. Deprotection of a compound of formula (C) by removal of the Boc group by any suitable process known in the art gives a compound of formula (3).

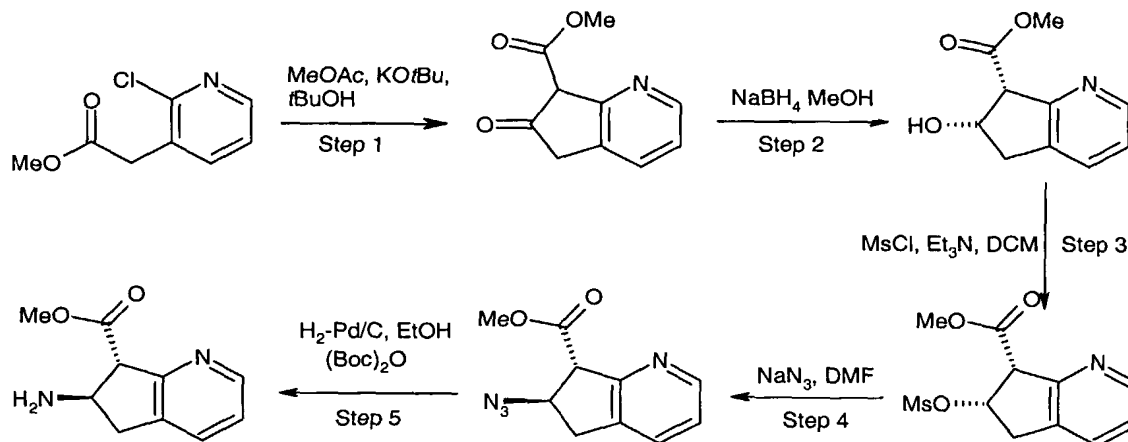
Suitable conditions for the above processes are exemplified in Intermediates 24 and 25 (compounds of formula (B)) and Intermediates 26, 27 and 31 (compounds of formula (C)). Intermediate 32 is an example of conversion of a compound of formula (C) wherein Y is -CH(CO₂R')₂ to a N-protected derivative of a compound of formula (3).

Compounds of the formula (B) are novel and provide a further independent aspect of the invention. Particular compounds of the formula (B) are those wherein r = 1. Further particular compounds of the formula (B) are those wherein A is phenylene. Still further particular compounds of the formula (B) are those wherein n = 0.

Compounds of the formula (3) where r = 1 and wherein A is heteroarylene can be prepared from suitably functionalised cycloalkyl fused heterocycles. For example, when A is pyridine,



compounds of formula (3b) and (3c) may be prepared from the corresponding pyridinone regioisomer according to Scheme 4 :-



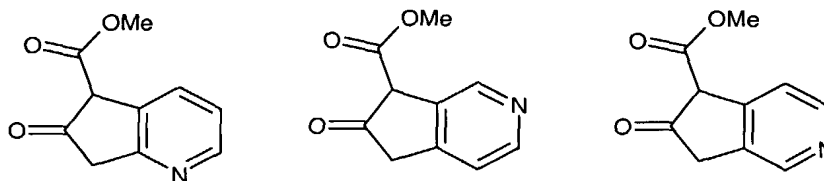
Scheme 4

Step 1 is performed on a compound known in the literature (Ger. Offen. 1997, 78).

Steps 2, 3, 4, and 5 are performed using standard techniques known in the art.

It will be appreciated the regioisomers of the beta-ketoesters (Scheme 5) would lead to the preparation of the four possible pyridyl regioisomers of the beta amino ester.

It will be appreciated that, in a similar manner, compounds of the formula (3) wherein A is heteroarylene containing a bridgehead nitrogen can be prepared from the appropriate suitably functionalised cycloalkyl fused heterocycles.



Scheme 5

It will be appreciated that the processes described above for formation and modification of Y as $\text{CH}_2\text{NR}^1\text{R}^2$ may be applied similarly whether to make the compound of formula (3) before coupling to the acid of formula (2) or whether to the product of such a coupling.

It will be appreciated that certain of the various ring substituents in the compounds of the present invention, for example R^1 may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions may convert one compound of the formula (1) into another compound of the formula (1). Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogen group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the

presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, *Protective Groups in Organic Synthesis*, John Wiley and Sons, 1991). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxy carbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxy carbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

Certain intermediates in the preparation of a compound of the formula (1) are novel and form another aspect of the invention.

As stated hereinbefore the compounds defined in the present invention possesses glycogen phosphorylase inhibitory activity. This property may be assessed, for example, using the procedure set out below.

Assay

The activity of the compounds is determined by measuring the inhibitory effect of the compounds on glycogen degradation, the production of glucose-1-phosphate from glycogen is monitored by the multienzyme coupled assay, as described in EP 0 846 464 A2, general method of Pesce et al (Pesce, M A, Bodourian, S H, Harris, R C, and Nicholson, J F (1977) Clinical Chemistry 23, 1171 - 1717). The reactions were in 384well microplate format in a volume of 50 μ l. The change in fluorescence due to the conversion of the co-factor NAD to NADH is measured at 340nm excitation, 465nm emission in a Tecan Ultra Multifunctional Microplate Reader. The reaction is in 50mM HEPES, 3.5mM KH₂PO₄, 2.5mM MgCl₂, 2.5mM ethylene glycol-bis(b-aminoethyl ether) *N,N,N',N'*-tetraacetic acid, 100mM KCl, 8mM D-(+)-glucose pH7.2, containing 0.5mM dithiothreitol, the assay buffer solution. Human recombinant liver glycogen phosphorylase *a* (hrl GP*a*) 20nM is pre-incubated in assay buffer solution with 6.25mM NAD, 1.25mg type III glycogen at 1.25 mg ml⁻¹ the reagent buffer, for 30 minutes. The coupling enzymes, phosphoglucomutase and glucose-6-phosphate dehydrogenase (Sigma) are prepared in reagent buffer, final concentration 0.25Units per well. 20 μ l of the hrl GP*a* solution is added to 10 μ l compound solution and the reaction started with the addition of 20ul coupling enzyme solution. Compounds to be tested are prepared in 10 μ l 5% DMSO in assay buffer solution, with final concentration of 1% DMSO in the assay. The non-inhibited activity of GP*a* is measured in the presence of 10 μ l 5% DMSO in assay

buffer solution and maximum inhibition measured in the presence of 5mgs ml⁻¹ N-ethylmaleimide. After 6 hours at 30°C Relative Fluoresence Units (RFUs) are measured at 340nm excitation, 465nm emission .

The assay is performed at a test concentration of inhibitor of 10µM or 100µM.

- 5 Compounds demonstrating significant inhibition at one or both of these concentrations may be further evaluated using a range of test concentrations of inhibitor to determine an IC₅₀, a concentration predicted to inhibit the enzyme reaction by 50%.

Activity is calculated as follows:-

- 10 % inhibition = (1 - (compound RFUs - fully inhibited RFUs)/ (non-inhibited rate RFUs - fully inhibited RFUs)) * 100.

Typical IC₅₀ values for compounds of the invention when tested in the above assay are in the range 100µM to 1nM. For example, Example 5 was found to have an IC₅₀ of 493nm.

- The inhibitory activity of compounds was further tested in rat primary hepatocytes. Rat hepatocytes were isolated by the collagenase perfusion technique, general method of
15 Seglen (P.O. Seglen, Methods Cell Biology (1976) 13 29-83). Cells were cultured on Nunclon six well culture plates in DMEM (Dulbecco's Modified Eagle's Medium) with high level of glucose containing 10% foetal calf serum, NEAA (non essential amino acids), Glutamine, penicillin /streptomycin ((100units/100ug)/ml) for 4 to 6 hours. The hepatocytes were then
20 cultured in the DMEM solution without foetal calf serum and with 10nM insulin and 10nM dexamethasone. Experiments were initiated after 18-20 hours culture by washing the cells and adding Krebs-Henseleit bicarbonate buffer containing 2.5mM CaCl₂ and 1% gelatin. The test compound was added and 5 minutes later the cells were challenged with 25nM glucagon. The Krebs-Henseleit solution was removed after 60 min incubation at 37°C , 95%O₂/5%CO₂ and the glucose concentration of the Krebs-Henseleit solution measured.

- 25 According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

- 30 The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for

example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

5 The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents. In one aspect, the compositions of the invention are in a form suitable for oral dosage.

10 Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as
15 ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

 Compositions for oral use may be in the form of hard gelatin capsules in which the
20 active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

 Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose,
25 methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters
30 derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or

condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl *p*-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavouring and/or colouring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable

solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing
5 finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

For further information on formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial
10 Board), Pergamon Press 1990.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active
15 agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial
20 Board), Pergamon Press 1990.

The compound of formula (1) will normally be administered to a warm-blooded animal at a unit dose within the range 5-5000 mg per square meter body area of the animal, i.e. approximately 0.1-100 mg/kg, and this normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 1-250 mg of
25 active ingredient. Preferably a daily dose in the range of 1-50 mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

The inhibition of glycogen phosphorylase activity described herein may be applied as a
30 sole therapy or may involve, in addition to the subject of the present invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. Simultaneous treatment may be in a single tablet or in separate tablets. For

example, in order to prevent, delay or treat type 2 diabetes mellitus, the compounds of the present invention or their pharmaceutically acceptable salts may be administered in combination with one or more of the following agent(s):

- 1) Insulin and insulin analogues;
- 5 2) Insulin secretagogues including sulphonylureas (for example glibenclamide, glipizide), prandial glucose regulators (for example repaglinide, nateglinide) and glucokinase activators
- 3) Agents that improve incretin action (for example dipeptidyl peptidase IV inhibitors, GLP-1 agonists)
- 10 4) Insulin sensitising agents including PPARgamma agonists (for example pioglitazone and rosiglitazone); and agents with combined PPARalpha and gamma activity
- 5) Agents that modulate hepatic glucose balance (for example metformin, fructose 1, 6 biphosphatase inhibitors, glycogen synthase kinase inhibitors, glucokinase activators)
- 6) Agents designed to reduce the absorption of glucose from the intestine (for example
- 15 acarbose);
- 7) Agents that prevent the reabsorption of glucose by the kidney (SGLT inhibitors)
- 8) Agents designed to treat the complications of prolonged hyperglycaemia (for example aldose reductase inhibitors)
- 9) Anti-obesity agents (for example sibutramine and orlistat);
- 20 10) Anti- dyslipidaemia agents such as, HMG-CoA reductase inhibitors (statins, eg pravastatin); PPAR α agonists (fibrates, eg gemfibrozil); bile acid sequestrants (cholestyramine); cholesterol absorption inhibitors (plant stanols, synthetic inhibitors); bile acid absorption inhibitors (IBATi) and nicotinic acid and analogues (niacin and slow release formulations);
- 25 11) Antihypertensive agents such as, β blockers (eg atenolol, inderal); ACE inhibitors (eg lisinopril); Calcium antagonists (eg. nifedipine); Angiotensin receptor antagonists (eg candesartan), α antagonists and diuretic agents (eg. furosemide, benzthiazide);
- 12) Haemostasis modulators such as, antithrombotics, activators of fibrinolysis and antiplatelet agents; thrombin antagonists; factor Xa inhibitors; factor VIIa inhibitors);
- 30 antiplatelet agents (eg. aspirin, clopidogrel); anticoagulants (heparin and Low molecular weight analogues, hirudin) and warfarin;
- 13) Agents which antagonise the actions of glucagon; and

14) Anti-inflammatory agents, such as non-steroidal anti-inflammatory drugs (eg. aspirin) and steroidal anti-inflammatory agents (eg. cortisone).

According to a further aspect of the present invention there is provided a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use in a method of treatment of a warm-blooded animal such as man by therapy.

According to an additional aspect of the invention there is provided a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use as a medicament.

10 According to an additional aspect of the invention there is provided a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use as a medicament in the treatment of type 2 diabetes, insulin resistance, syndrome X, hyperinsulinaemia, hyperglucagonaemia, cardiac ischaemia or obesity in a warm-blooded animal such as man.

15 According to this another aspect of the invention there is provided the use of a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of type 2 diabetes, insulin resistance, syndrome X, hyperinsulinaemia, hyperglucagonaemia, cardiac ischaemia or obesity in a warm-blooded animal such as man.

20 According to this another aspect of the invention there is provided the use of a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of type 2 diabetes in a warm-blooded animal such as man.

According to a further feature of this aspect of the invention there is provided a method of producing a glycogen phosphorylase inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (1).

According to this further feature of this aspect of the invention there is provided a method of treating type 2 diabetes, insulin resistance, syndrome X, hyperinsulinaemia, hyperglucagonaemia, cardiac ischaemia or obesity in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (1).

According to this further feature of this aspect of the invention there is provided a method of treating type 2 diabetes in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (1).

5 As stated above the size of the dose required for the therapeutic or prophylactic treatment of a particular cell-proliferation disease will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. A unit dose in the range, for example, 1-100 mg/kg, preferably 1-50 mg/kg is envisaged.

10 In addition to their use in therapeutic medicine, the compounds of formula (1) and their pharmaceutically acceptable salts are also useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of cell cycle activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

15 In the above other pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred embodiments of the compounds of the invention described herein also apply.

Examples

20 The invention will now be illustrated by the following examples in which, unless stated otherwise:

(i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25°C and under an atmosphere of an inert gas such as argon;

25 (ii) organic solutions were dried over anhydrous magnesium sulphate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30 mmHg) with a bath temperature of up to 60°C;

(iii) chromatography means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates; where a Bond Elut column is referred to, this means a column containing 10 g or 20 g or 50 g of silica of 40 micron particle size, the silica being contained in a 60 ml disposable syringe and supported by a porous disc, obtained from
30 Varian, Harbor City, California, USA under the name "Mega Bond Elut SI"; "Mega Bond Elut" is a trademark; where a Biotage cartridge is referred to this means a cartridge containing

KP-SIL™ silica, 60μ, particle size 32-63mM, supplied by Biotage, a division of Dyax Corp., 1500 Avon Street Extended, Charlottesville, VA 22902, USA;

(iv) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;

5 (v) yields are given for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;

(vi) where given, NMR data is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300 MHz using perdeuterio dimethyl sulphoxide (DMSO-δ₆) as solvent unless

10 otherwise indicated, other solvents (where indicated in the text) include deuterated chloroform CDCl₃;

(vii) chemical symbols have their usual meanings; SI units and symbols are used;

(viii) reduced pressures are given as absolute pressures in Pascals (Pa); elevated pressures are given as gauge pressures in bars;

15 (ix) solvent ratios are given in volume : volume (v/v) terms;

(x) mass spectra (MS) were run with an electron energy of 70 electron volts in the chemical ionisation (CI) mode using a direct exposure probe; where indicated ionisation was effected by electron impact (EI), fast atom bombardment (FAB) or electrospray (ESP); values for m/z are given; generally, only ions which indicate the parent mass are reported and unless

20 otherwise stated the value quoted is (M-H)⁻;

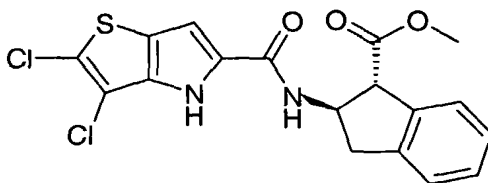
(xi) The following abbreviations are used:

SM	starting material;
EtOAc	ethyl acetate;
MeOH	methanol;
25 EtOH	ethanol;
DCM	dichloromethane;
HOBT	1-hydroxybenzotriazole;
DIPEA	di-isopropylethylamine;
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
30	hydrochloride;
Et ₂ O	diethyl ether;
THF	tetrahydrofuran;

	DMF	<i>N,N</i> -dimethylformamide;
	HATU	<i>O</i> -(7-Azabenzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluroniumhexafluorophosphate
5	EDAC	1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride
	TFA	Trifluoroacetic acid
	DMTMM	4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride
	DMA	<i>N,N</i> -dimethylacetamide
10	NaHCO ₃	Sodium bicarbonate
	mCPBA	meta-chloroperbenzoic acid
	RT	retention time

Certain intermediates described hereinafter within the scope of the invention may also possess useful activity, and are provided as a further feature of the invention. Particular examples of such intermediates are Intermediates 52 and 53, each of which are provided as a further independent aspect of the invention.

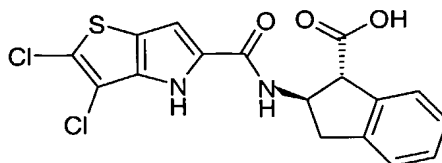
Example 1 : Methyl (1*R*,2*R*)-2-[[(2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrol-5-yl)carbonyl]amino]indane-1-carboxylate



Methyl (1*R*,2*R*)-2-aminoindane-1-carboxylate trifluoroacetic acid salt (**Intermediate 5**; 1.8 g, 5.9 mmol), 2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylic acid (**Intermediate 3**; 1.4g, 5.9 mmol) and DIPEA (2.0 mL, 11.8 mmol) were dissolved in DCM (25 mL). HOBt (796mg, 5.9 mmol) and EDCI (1.4g, 7.4 mmol) were added and the mixture stirred at ambient temperature for 2 h. The volatiles were removed under reduced pressure and the residue dissolved in ethyl acetate (50 mL), washed with water (2 x 25 mL), brine (25 mL), dried (MgSO₄) and the volatiles removed under reduced pressure. The crude residue was purified by silica gel chromatography (3:1, *iso*-hexane:ethyl acetate) to give the title compound (1.7g, 71%) as a pale yellow foam.

¹H NMR (CDCl₃) δ: 2.98 (dd, 1H), 3.62 (dd, 1H), 4.15 (d, 1H), 5.2 (m, 1H), 6.36 (d, 1H), 6.65 (s, 1H), 7.3 (m, 4H), 10.02 (s, 1H); MS m/z 407/409 (M-H).

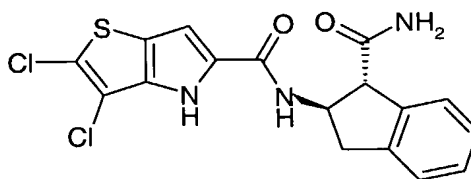
Example 2: (1*R*,2*R*)-2-[[2,3-Dichloro-4*H*-thieno[3,2-*b*]pyrrol-5-yl)carbonyl]amino}indane-1-carboxylic acid



Methyl (1*R*,2*R*)-2-[[2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrol-5-yl)carbonyl]amino}indane-1-carboxylate (**Example 1**; 1.0g, 3.18 mmol) was dissolved in THF (10 mL), hydrochloric acid (2.0 mL, 6M aqueous) added and the mixture stirred at 60 °C for 30 h. Evaporation of the volatiles under reduced pressure gave the title compound (1.1 g, 88%) as a pale brown foam.

¹H NMR δ: 2.95 (dd, 1H), 3.38 (dd, 1H), 4.08 (d, 1H), 4.95 (m, 1H), 7.1 (s, 1H), 7.25 (m, 4H), 8.57 (d, 1H), 12.35 (s, 1H), 12.56 (s, 1H); MS m/z 395, 397, 399.

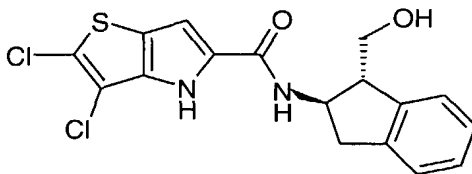
Example 3: *N*-[(1*R*,2*R*)-1-(Aminocarbonyl)-2,3-dihydro-1*H*-inden-2-yl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide



tert-Butyl [(1*R*,2*R*)-1-(aminocarbonyl)-2,3-dihydro-1*H*-inden-2-yl]carbamate (**Intermediate 15**; 75 mg, 0.27 mmol) was dissolved in TFA (2 mL) and stirred at ambient temperature for 2 h, the volatiles removed by evaporation under reduced pressure and the crude residue co-evaporated with CHCl₃ (2 x 2 mL). The residue was dissolved in DCM (5 mL), 2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylic acid (**Intermediate 3**; 63.0mg, 0.27 mmol), DIPEA (94μl, 0.54 mmol), HOBT (36mg, 0.27 mmol) and EDCI (65mg, 0.34 mmol) added and the mixture stirred at ambient temperature for 20 h. The volatiles were removed under reduced pressure and the residue dissolved in ethyl acetate (10 mL), washed with water (2 x 5 mL), brine (5 mL), dried (MgSO₄) and the volatiles removed under reduced pressure. The crude residue was purified by flash silica gel chromatography (2:1, ethyl acetate:iso-hexane) to give the title compound (50mg, 47%) as a pale yellow solid.

$^1\text{H NMR } \delta$: 2.95 (dd, 1H), 3.38 (dd, 1H), 3.6 (m, 2H), 3.98 (d, 1H), 4.93 (m, 1H), 7.1 (s, 1H), 7.24 (m, 4H), 7.63 (s, 1H), 8.5 (d, 1H); MS m/z 394, 396, 398.

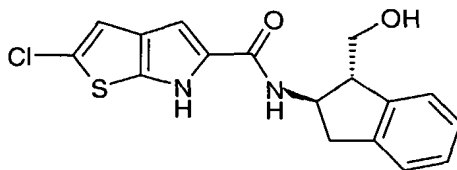
Example 4: 2,3-Dichloro-*N*-[(1*R*,2*R*)-1-(hydroxymethyl)-2,3-dihydro-1*H*-inden-2-yl]-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide



N-[(1*R*,2*R*)-1-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-2,3-dihydro-1*H*-inden-2-yl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide (**Intermediate 16**; 286mg, 0.56 mmol) was dissolved in THF (5 mL), tetrabutylammonium fluoride (2 mL, 1M in THF, 2.0 mmol) added and the mixture stirred at ambient temperature for 2 h. The volatiles were removed under reduced pressure and the residue dissolved in ethyl acetate (15 mL), washed with water (2 x 5 mL), brine (5 mL), dried (MgSO_4) and the solvent removed under reduced pressure. The crude residue was crystallized (ethyl acetate) to give the title compound (120 mg, 57%) as a colourless solid.

$^1\text{H NMR } \delta$: 2.9 (dd, 1H), 3.3 (m, 1H), 3.68 (m, 2H), 4.55 (m, 1H), 4.75 (t, 1H), 7.2 (m, 4H), 7.39 (m, 1H), 8.5 (d, 1H), 12.35 (s, 1H); MS m/z 381, 383, 385.

Example 5: 2-Chloro-*N*-[(1*R*,2*R*)-1-(hydroxymethyl)-2,3-dihydro-1*H*-inden-2-yl]-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide



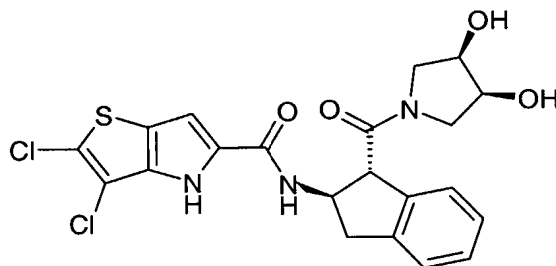
N-[(1*R*,2*R*)-1-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-2,3-dihydro-1*H*-inden-2-yl]-2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide (**Intermediate 17**; 320 mg, 0.7 mmol) was dissolved in THF (10 mL), tetrabutylammonium fluoride (5 mL, 1M in THF, 5.0 mmol) added and the mixture stirred at ambient temperature for 4 h. The volatiles were removed under reduced pressure and the residue dissolved in ethyl acetate (15 mL), washed with water (2x5 mL), brine (5 mL), dried (MgSO_4) and the solvent removed under reduced pressure. The crude

residue was crystallized (ethyl acetate:*iso*-hexane, 1:1) to give the title compound (160 mg, 66%) as a colourless solid.

¹H NMR δ : 2.93 (dd, 1H), 3.32 (m, 1H), 3.73 (m, 2H), 4.55 (m, 1H), 4.8 (t, 1H), 7.1 (s, 1H), 7.22 (m, 4H), 7.4 (m, 1H), 8.45 (d, 1H), 11.9 (s, 1H); MS m/z 345, 347.

5

Example 6: 2,3-Dichloro-N-((1R,2R)-1-[(3R,4S)-3,4-dihydroxypyrrolidin-1-yl]carbonyl)-2,3-dihydro-1H-inden-2-yl)-4H-thieno[3,2-b]pyrrole-5-carboxamide



(1R,2R)-2-[[[(2,3-dichloro-4H-thieno[3,2-b]pyrrol-5-yl)carbonyl]amino]indane-1-carboxylic acid (**Example 2**; 99 mg, 0.25 mmol), (3aR, 6aS)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyrrole (36mg, 0.25 mmol) and DIPEA (44 μ l, 0.25 mmol) were dissolved in DCM (5mL). HOBt (34 mg, 0.25 mmol) and EDCI (60 mg, 0.313 mmol) were added and the mixture stirred at ambient temperature for 6 h. The volatiles were removed under reduced pressure and the residue dissolved in ethyl acetate (15 mL), washed with water (2 x 5 mL),
15 brine (5 mL), dried (MgSO₄) and the solvent removed under reduced pressure. The residue was dissolved in ethanol (3 mL), hydrochloric acid (0.2 mL, 2M aqueous) added, and the solution stirred at ambient temperature for 4 h. The volatiles were removed under reduced pressure to give the title compound (70 mg, 58%) as a pale yellow foam.

¹H NMR δ : 2.95 (dd, 1H), 3.4 (m, 4H), 3.83 (m, 1H), 4.1 (m, 4H), 4.42 (m, 1H), 4.9 (m, 1H),
20 7.17 (m, 5H), 8.6 (m, 1H), 12.4 (m, 1H); MS m/z 480, 482.

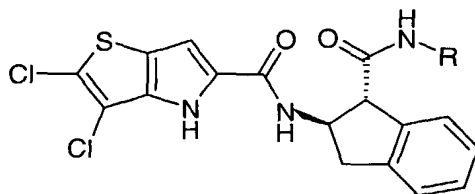
The following examples were made by a similar process to **Example 6** using (1R,2R)-2-[[[(2,3-dichloro-4H-thieno[3,2-b]pyrrol-5-yl)carbonyl]amino]indane-1-carboxylic acid (**Example 2**) and the appropriate commercially available amine.

25

Example 7: 2,3-Dichloro-N-((1*R*,2*R*)-1-[(2,3-dihydroxypropyl)amino]carbonyl)-2,3-dihydro-1*H*-inden-2-yl)-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide

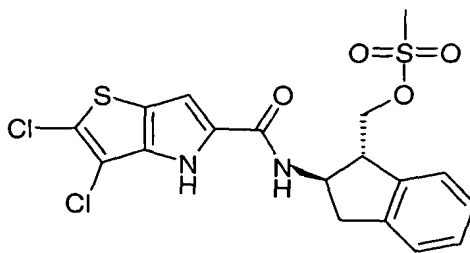
Example 8: 2,3-dichloro-N-((1*R*,2*R*)-1-[(2-hydroxyethyl)amino]carbonyl)-2,3-dihydro-1*H*-inden-2-yl)-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide

5 **Example 9: 2,3-Dichloro-N-((1*R*,2*R*)-1-[(glycinamide)carbonyl]-2,3-dihydro-1*H*-inden-2-yl)-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide**



Ex	R	<u>NMR</u>	<u>M/z</u>
7		3.05 (m, 2H), 3.22 (m, 1H), 3.4 (m, 3H), 3.6 (m, 1H), 4.13 (d, 1H), 5.0 (m, 1H), 7.2 (s, 1H), 7.3 (m, 4H), 8.32 (m, 1H), 8.65 (d, 1H), 12.5 (s, 1H)	466, 468, 470 (M-H)
8		2.97 (dd, 1H), 3.3 (m, 5H), 4.0 (d, 1H), 4.63 (m, 1H), 4.95 (m, 1H), 7.1 (s, 1H), 7.2 (m, 4H), 8.2 (m, 1H), 8.5 (d, 1H), 12.33 (s, 1H)	438, 440, 442
9		2.98 (dd, 1H), 3.36 (m, 1H), 3.7 (m, 2H), 4.07 (d, 1H), 4.93 (m, 1H), 6.96 (s, 1H), 7.1 (s, 1H), 7.22 (m, 5H), 8.42 (m, 1H), 8.6 (d, 1H), 12.32 (s, 1H)	451, 453, 455

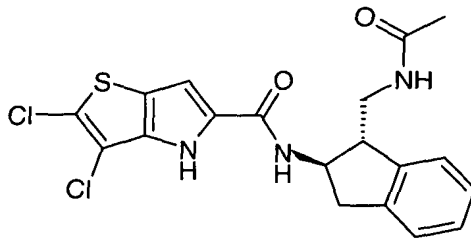
Example 10: ((1*R*,2*R*)-2-[[2,3-Dichloro-4*H*-thieno[3,2-*b*]pyrrol-5-yl]carbonyl]amino)-2,3-dihydro-1*H*-inden-1-yl)methyl methanesulfonate



2,3-Dichloro-*N*-[(1*R*,2*R*)-1-(hydroxymethyl)-2,3-dihydro-1*H*-inden-2-yl]-4*H*-thieno[3,2-
 5 *b*]pyrrole-5-carboxamide (**Example 4**; 1.2 g, 3.15 mmol) and triethylamine (658 μ l, 4.73 mmol) were dissolved in THF (20 mL). Methanesulphonyl chloride (397 mg, 3.47 mmol) in THF (5 mL) was added and the mixture stirred at ambient temperature for 3h. The volatiles were removed under reduced pressure and the residue dissolved in ethyl acetate (50 mL), washed with water (2x10 mL), brine (10 mL), dried (MgSO₄) and the solvent removed under
 10 reduced pressure to give the title compound (1.45 g, 100%) as a pale brown foam.

¹H NMR (CDCl₃) δ : 2.95 (dd, 1H), 3.5 (dd, 1H), 3.62 (m, 1H), 4.45 (dd, 1H), 4.65 (dd, 1H), 4.8 (m, 1H), 6.4 (d, 1H), 6.75 (s, 1H), 7.25 (m, 4H), 9.8 (s, 1H); MS *m/z* 481, 483 (M+Na).

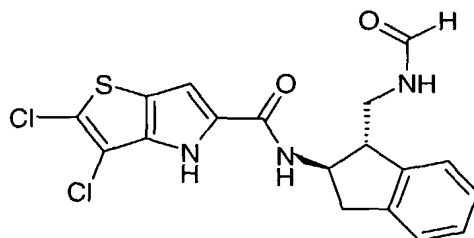
Example 11: *N*-[(1*S*,2*R*)-1-[(Acetylamino)methyl]-2,3-dihydro-1*H*-inden-2-yl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide



15 *N*-[(1*S*,2*R*)-1-(Aminomethyl)-2,3-dihydro-1*H*-inden-2-yl]-2,3-dichloro-4*H*-thieno[3,2-
b]pyrrole-5-carboxamide (**Intermediate 18**; 115 mg, 0.3 mmol), acetic acid (36 μ l, 0.6 mmol) and DIPEA (52 μ l, 0.3 mmol) were dissolved in DCM (2.5 mL). HOBT (41 mg, 0.3 mmol) and EDCI (72 mg, 0.375 mmol) were added and the mixture stirred at ambient temperature for
 20 24 h. The volatiles were removed under reduced pressure and the residue dissolved in ethyl acetate (25 mL), washed with water (2 x 10 mL), brine (10 mL), dried (MgSO₄) and the solvent removed under reduced pressure. The crude residue was purified by flash silica gel chromatography (2:1, ethyl acetate:*iso*-hexane) to give the title compound (1.45 g, 100%) as a pale brown foam.

¹H NMR δ : 1.8 (s, 3H), 2.9 (dd, 1H), 3.3 (m, 4H), 4.45 (m, 1H), 7.1 (s, 1H), 7.22 (m, 4H), 7.94 (m, 1H), 8.43 (d, 1H), 12.31 (s, 1H); MS m/z 422, 424, 426.

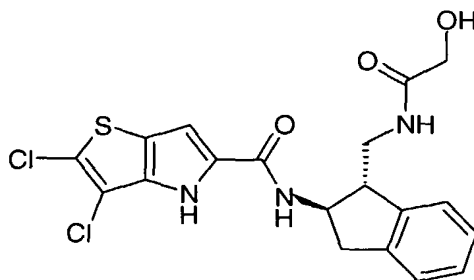
Example 12: 2,3-Dichloro-*N*-[(1*S*,2*R*)-1-[(formylamino)methyl]-2,3-dihydro-1*H*-inden-2-yl]-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide



N-[(1*S*,2*R*)-1-(Aminomethyl)-2,3-dihydro-1*H*-inden-2-yl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide (**Intermediate 18**; 115 mg, 0.3 mmol), formic acid (14 mg, 0.3 mmol) and DIPEA (52 μ l, 0.3 mmol) were dissolved in DCM (2.5 mL). HOBT (41 mg, 0.3 mmol) and EDCI (72 mg, 0.375 mmol) were added and the mixture stirred at ambient temperature for 24 h. The volatiles were removed under reduced pressure and the residue dissolved in ethyl acetate (25 mL), washed with water (2 x 10 mL), brine (10 mL), dried (MgSO₄) and the solvent removed under reduced pressure. The crude residue was purified by flash silica gel chromatography (1:1, ethyl acetate:*iso*-hexane) to give the title compound (95 mg, 77%) as a colourless foam.

¹H NMR δ : 2.9 (dd, 1H), 3.4 (m, 4H), 4.5 (m, 1H), 7.15 (s, 1H), 7.25 (m, 4H), 8.05 (s, 1H), 8.12 (s, 1H), 8.48 (d, 1H), 12.35 (s, 1H); MS m/z 408, 410, 412.

Example 13: 2,3-Dichloro-*N*-[(1*S*,2*R*)-1-[(glycoloylamino)methyl]-2,3-dihydro-1*H*-inden-2-yl]-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide

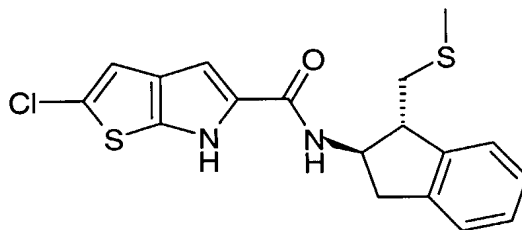


N-[(1*S*,2*R*)-1-(Aminomethyl)-2,3-dihydro-1*H*-inden-2-yl]-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide (**Intermediate 18**; 1.2g, 3.2 mmol), acetoxyacetic acid (373 mg, 3.2 mmol) and HOBT (432 mg, 3.2 mmol) were dissolved in DCM (20 mL). EDCI (767 mg, 4.0

mmol) was added and the mixture stirred at ambient temperature for 3 h. The volatiles were removed under reduced pressure and the residue dissolved in ethyl acetate (50 mL), washed with water (2 x 20 mL), brine (20 mL), dried (MgSO₄) and the solvent removed under reduced pressure. The residue was dissolved in THF:MeOH (1:1, 30 mL), K₂CO₃ (1.0g) added and the mixture stirred at ambient temperature for 1 h. The volatiles were removed under reduced pressure and the residue dissolved in ethyl acetate (50 mL), washed with water (3x20 mL), brine (20 mL), dried (MgSO₄) and the solvent removed under reduced pressure. The resulting residue was purified by flash silica gel chromatography (ethyl acetate) to give the title compound (1.05 g, 75%) as a cream powder.

¹H NMR δ : 2.9 (dd, 1H), 3.25 (dd, 1H), 3.38 (m, 1H), 3.45 (m, 2H), 3.78 (s, 2H), 4.48 (m, 1H), 5.4 (s, 1H), 7.13 (s, 1H), 7.2 (m, 4H), 7.8 (m, 1H), 8.45 (d, 1H), 12.32 (s, 1H); MS m/z 438, 440, 442.

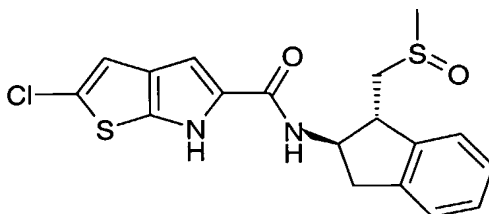
Example 14: 2,3-Dichloro-N-((1S,2R)-1-[(methylthio)amino]methyl)-2,3-dihydro-1H-inden-2-yl)-4H-thieno[3,2-b]pyrrole-5-carboxamide



((1R,2R)-2-[[2-Chloro-6H-thieno[2,3-b]pyrrol-5-yl]carbonyl]amino)-2,3-dihydro-1H-inden-1-yl)methyl methanesulfonate (**Intermediate 19**; 800 mg, 1.9 mmol) was dissolved in anhydrous dimethylacetamide (10 mL), sodium methane thiolate (147 mg, 2.1 mmol) added and the mixture stirred at ambient temperature for 24 h. Citric acid (10 mL, 2M aqueous) was added and the mixture extracted with ethyl acetate (30 mL), washed with water (2 x 10 mL), brine (10 mL), dried (MgSO₄), filtered and the volatiles removed under reduced pressure. The crude residue was purified by flash silica gel chromatography (4:1, *iso*-hexane:ethyl acetate) to give the title compound (560 mg, 78%) as a pale yellow solid.

¹H NMR (CDCl₃) δ : 2.18 (s, 3H), 2.95 (m, 3H), 3.4 (m, 1H), 3.58 (dd, 1H), 4.75 (m, 1H), 6.35 (d, 1H), 6.62 (s, 1H), 7.25 (m, 3H), 7.38 (m, 1H), 10.79 (s, 1H); MS m/z 375, 377 (M-H).

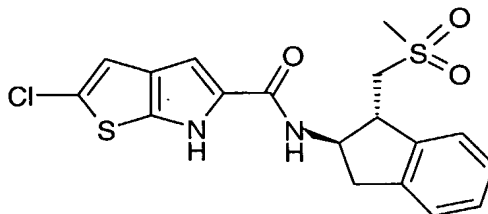
Example 15: 2-Chloro-N-((1*R*,2*R*)-1-[(methylsulfinyl)methyl]-2,3-dihydro-1*H*-inden-2-yl)-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide



2,3-Dichloro-N-((1*S*,2*R*)-1-[(methylthio)amino]methyl)-2,3-dihydro-1*H*-inden-2-yl)-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide (**Example 14**; 1.0 g, 2.65 mmol) was dissolved in methanol:THF (1:1, 10 mL), oxone (205 mg, 0.33 mmol) added and the mixture stirred at ambient temperature for 3 h. The mixture was poured into water (25 mL) and extracted with ethyl acetate (2 x 20 mL). The organic extract was washed with water (20 mL), brine (20 mL), dried (MgSO₄) and the volatiles removed under reduced pressure. The crude residue was purified by flash silica gel chromatography (19:1, ethyl acetate:methanol) to give the title compound (250 mg, 24%) as a colourless solid.

¹H NMR δ: 2.58 (s, 1.5H), 2.62 (s, 1.5H), 3.1 (m, 3H), 3.65 (m, 1H), 4.55 (m, 1H), 7.02 (m, 1H), 7.15 (s, 1H), 7.22 (m, 3H), 7.37 (m, 1H), 8.48 (m, 1H), 11.83 (s, 1H); MS m/z 391, 393.

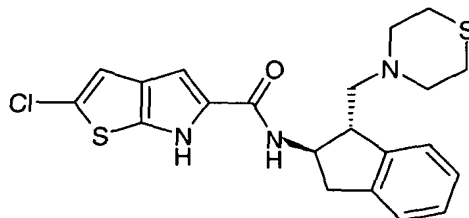
Example 16: 2-Chloro-N-((1*R*,2*R*)-1-[(methylsulfonyl)methyl]-2,3-dihydro-1*H*-inden-2-yl)-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide



2,3-Dichloro-N-((1*S*,2*R*)-1-[(methylthio)amino]methyl)-2,3-dihydro-1*H*-inden-2-yl)-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide (**Example 14**; 250 mg, 0.663 mmol) was dissolved in methanol:THF (1:1, 10 mL), oxone (410mg, 0.663 mmol) added and the mixture stirred at ambient temperature for 24 h. The mixture was poured into water (25 mL) and extracted with ethyl acetate (2 x 20 mL). The organic extract was washed with water (20 mL), brine (20 mL), dried (MgSO₄) and the volatiles removed under reduced pressure. The crude residue was purified by flash silica gel chromatography (1:1, ethyl acetate:*iso*-hexane) to give the title compound (200 mg, 74%) as a colourless solid.

¹H NMR δ : 2.94 (dd, 1H), 3.06 (s, 3H), 3.25 (m, 1H), 3.55 (m, 2H), 4.75 (m, 1H), 4.59 (m, 1H), 7.0 (s, 1H), 7.15 (s, 1H), 7.22 (m, 3H), 7.48 (m, 1H), 8.44 (d, 1H), 11.84 (s, 1H); MS m/z 407/409.

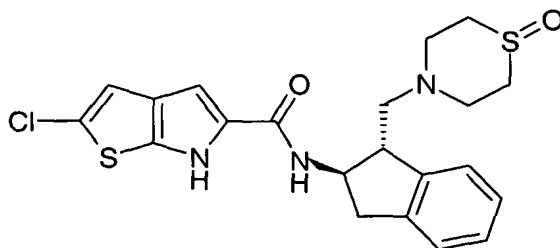
5 **Example 17: 2-Chloro-N-[(1S,2R)-1-(thiomorpholin-4-ylmethyl)-2,3-dihydro-1H-inden-2-yl]-6H-thieno[2,3-b]pyrrole-5-carboxamide**



10 ((1R,2R)-2-[[2-Chloro-6H-thieno[2,3-b]pyrrol-5-yl]carbonyl]amino)-2,3-dihydro-1H-inden-1-yl)methyl methanesulfonate (**Intermediate 19**; 800 mg, 1.92 mmol), thiomorpholine (1.98 g, 19.2 mmol) and DIPEA (1.36 g, 8.0 mmol) in acetonitrile (20 mL) was heated in a microwave reactor at 150 °C for 5 mins. The volatiles were removed under reduced pressure and the residue dissolved in ethyl acetate (35 mL), washed with water (2 x 20 mL), brine (20 mL), dried (MgSO₄) and the solvent removed under reduced pressure. The crude residue was purified by flash silica gel chromatography (2:1, iso-hexane:ethyl acetate) to give the title
15 compound (440 mg, 53%) as a pale yellow solid.

¹H NMR δ : 2.57 (m, 4H), 2.7 (m, 4H), 2.83 (dd, 1H), 3.22 (m, 3H), 3.41 (m, 1H), 4.43 (m, 1H), 7.2 (s, 1H), 7.17 (m, 4H), 7.4 (m, 1H), 8.28 (d, 1H), 11.81 (s, 1H); MS m/z 432, 434.

20 **Example 18: 2-Chloro-N-[(1S,2R)-1-[(1-oxidothiomorpholin-4-yl)methyl]-2,3-dihydro-1H-inden-2-yl]-6H-thieno[2,3-b]pyrrole-5-carboxamide**

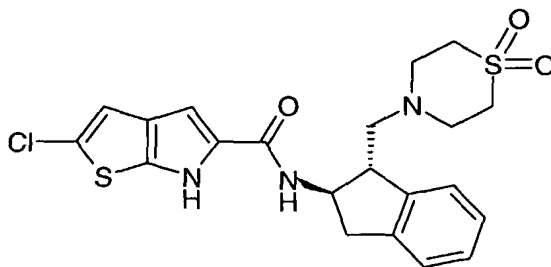


2-Chloro-N-[(1S,2R)-1-(thiomorpholin-4-ylmethyl)-2,3-dihydro-1H-inden-2-yl]-6H-thieno[2,3-b]pyrrole-5-carboxamide (**Example 17**; 180 mg, 0.417 mmol) was dissolved in 1:1 methanol:THF (5 mL), oxone (127.5 mg, 0.21 mmol) added and the mixture stirred at ambient

temperature for 24 h. The mixture was poured into water (10 mL) and extracted with ethyl acetate (2 x 10 mL). The organic extract was washed with water (10 mL), brine (10 mL), dried (MgSO₄) and the volatiles removed under reduced pressure. The crude residue was purified by flash silica gel chromatography (19:1, ethyl acetate:methanol) to give the title compound (85 mg, 46%) as a colourless solid.

¹H NMR δ: 2.56 (m, 1H), 2.7 (m, 5H), 2.9 (m, 5H), 3.25 (m, 1H), 3.41 (m, 1H), 4.27 (m, 1H), 7.01 (s, 1H), 7.17 (m, 4H), 7.4 (m, 1H), 8.3 (d, 1H), 11.82 (s, 1H); MS m/z 448, 450.

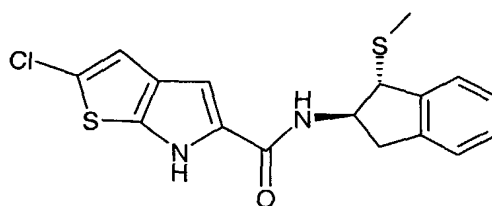
Example 19: 2-Chloro-N-[(1*S*,2*R*)-1-[(1,1-dioxidothiomorpholin-4-yl)methyl]-2,3-dihydro-1*H*-inden-2-yl]-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide



2-Chloro-N-[(1*S*,2*R*)-1-(thiomorpholin-4-ylmethyl)-2,3-dihydro-1*H*-inden-2-yl]-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide (**Example 17**; 280 mg, 0.65 mmol) was dissolved in anhydrous THF (10 mL), *m*-chloroperbenzoic acid (373 mg, 1.3 mmol) added and the mixture stirred at ambient temperature for 24 h. The volatiles were removed under reduced pressure and the residue dissolved in ethyl acetate (20 mL), washed with water (2x5 mL), brine (10 mL), dried (MgSO₄) and the solvent removed under reduced pressure. The crude residue was purified by flash silica gel chromatography (9:1, DCM:methanol) to give the title compound (190 mg, 63%) as a colourless solid.

¹H NMR δ: 2.95 (m, 9H), 3.17 (d, 2H), 3.35 (m, 1H), 3.55 (m, 1H), 4.05 (m, 1H), 7.05 (s, 1H), 7.14 (s, 1H), 7.27 (m, 3H), 7.58 (m, 1H), 8.54 (d, 1H), 11.87 (s, 1H); MS m/z 464, 466.

Example 20: (+/-)-trans-2-Chloro-N-[1-(methylthio)-2,3-dihydro-1*H*-inden-2-yl]-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide



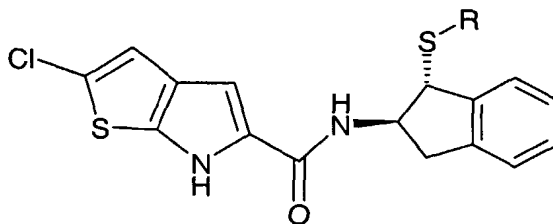
Ethylene glycol (4 mL), water (3 mL) and 8M potassium hydroxide (1 mL) was added to (+/-)-*trans*-Ethyl [-1-(methylthio)-2,3-dihydro-1*H*-inden-2-yl]carbamate (**Intermediate 20**, 200 mg, 0.80 mmol) and the reaction was heated to 100 °C for 1 h then at 110 °C for 16 h. The residue was taken up in ether (30 mL) and water (10 mL) and the organic layer was dried (MgSO₄), filtered and evaporated which was used in the subsequent coupling without further purification. 2-Chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxylic acid (**Intermediate 4**, 113 mg, 0.56 mmol), DCM (10 mL), HOBt (86 mg, 0.56 mmol), DIPEA (0.12 mL, 0.70 mmol) and EDCI (134 mg, 0.70 mmol) was added to the residue obtained from the first step and the reaction was stirred at ambient temperature for 16 h. The reaction was diluted with DCM (50 mL), extracted with 1M HCl (aqueous) (15 mL) then saturated aqueous NaHCO₃ (20 mL) and the organic layer was dried (MgSO₄), filtered and evaporated. Purification by column chromatography (Eluent: 1:4 to 1:2 EtOAc:hexanes) afforded the title compound (120 mg, 59% over 2 steps) as a white solid.

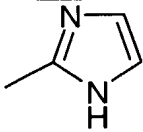
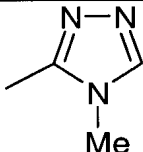
¹H NMR (DMSO) δ: 2.95 (dd, 1H), 3.39 (dd, 1H), 4.31 (d, 1H), 4.68 (m, 1H), 7.01 (s, 1H), 7.16 (s, 1H), 7.28 (m, 3H), 7.33 (m, 1H), 8.50 (d, 1H), 11.88 (s, 1H); MS m/z 361, 363 [M-H]⁻.

The following examples were made by the same 2-step process as **Example 20**, using 2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxylic acid (**Intermediate 4**) and the corresponding amines (**Intermediate 21** or **Intermediate 22**).

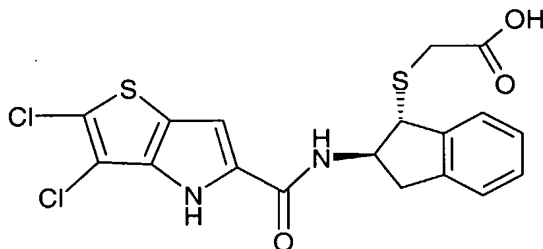
Example 21: (+/-)-*trans*-2,3-Dichloro-*N*-[-1-(1*H*-imidazol-2-ylthio)-2,3-dihydro-1*H*-inden-2-yl]-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide

Example 22: (+/-)-*trans* -2,3-Dichloro-*N*-[-1-[(4-methyl-4*H*-1,2,4-triazol-3-yl)thio]-2,3-dihydro-1*H*-inden-2-yl]-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide



Example	R	¹ H NMR	M/z
21		2.93 (dd, 1H), 3.35 (m, 1H), 4.67 (m, 1H), 4.92 (d, 1H), 7.15 (m, 8H), 8.68 (d, 1H), 11.90 (s, 1H), 12.45 (s, 1H).	415, 417
22		2.95 (dd, 1H), 3.35 (dd, 1H), 3.55 (s, 3H), 4.74 (m, 1H), 5.02 (d, 1H), 6.97 (s, 1H), 7.25 (m, 4H), 8.55 (m, 2H), 11.85 (s, 1H).	430, 432

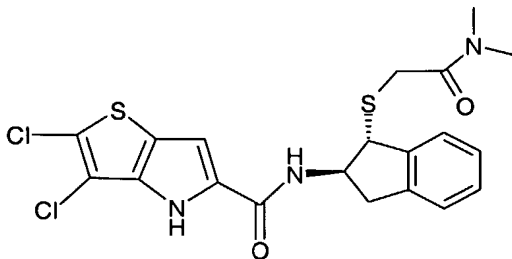
Example 23: [(((1*R*,2*R*)-2-[[2,3-Dichloro-4*H*-thieno[3,2-*b*]pyrrol-5-yl)carbonyl]amino}-2,3-dihydro-1*H*-inden-1-yl)thio]acetic acid



Lithium hydroxide (300 mg, 7.16 mmol) was added to methyl [(((1*R*,2*R*)-2-[[2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrol-5-yl)carbonyl]amino}-2,3-dihydro-1*H*-inden-1-yl)thio]acetate (**Intermediate 29**, 1.63 g, 3.58 mmol) in THF:water (4:1, 50 mL) and stirred at ambient temperature for 2.5 h. The reaction was acidified (pH=1) with 1M HCl (aqueous) and extracted with EtOAc (2 x 30 mL) and the organic layer was dried (MgSO₄), filtered and evaporated to afford the title compound (1.60 g, 100%) as a foamy solid.

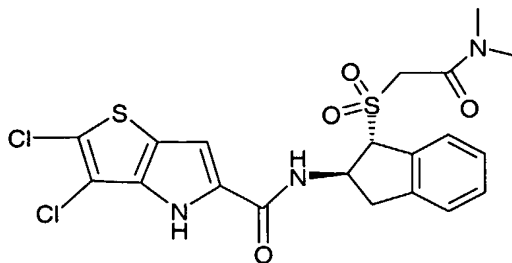
¹H NMR (DMSO) δ: 2.93 (dd, 1H), 3.41 (m, 2H), 3.62 (d, 1H), 4.45 (m, 1H), 4.63 (m, 1H), 7.10 (s, 1H), 7.30 (m, 4H), 8.58 (d, 1H), 12.35 (s, 1H). MS m/z 463, 465 [M + Na]⁺.

Example 24: 2,3-Dichloro-*N*-((1*R*,2*R*)-1-{[2-(dimethylamino)-2-oxoethyl]thio}-2,3-dihydro-1*H*-inden-2-yl)-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide



Dimethylamine (0.68 mL, 2.0M in THF, 1.36 mmol), DIPEA (0.16 mL, 0.91 mmol) and
 5 HBTU (378 mg, 0.10 mmol) was added to a stirred solution of [((1*R*,2*R*)-2-{[(2,3-Dichloro-4*H*-thieno[3,2-*b*]pyrrol-5-yl)carbonyl]amino}-2,3-dihydro-1*H*-inden-1-yl)thio]acetic acid
 (Example 23; 400 mg, 0.91 mmol) in DCM (10 mL) and the reaction was stirred at ambient
 temperature for 2 h. The reaction was quenched by addition of saturated aqueous NaHCO₃ (20
 mL) and diluted with DCM (20 mL). The organic layer was separated and washed with 1M
 10 HCl (aqueous) (15 mL), dried (MgSO₄), filtered and the volatiles removed *in vacuo*.
 Purification by column chromatography (eluent gradient: 1:1 EtOAc:hexanes to EtOAc)
 afforded the title compound (349 mg, 82%) as a white foam.
¹H NMR (DMSO) δ: 2.78 (s, 3H), 2.91 (dd, 1H), 2.95 (s, 3H), 3.38 (m, 1H), 3.63 (s, 2H), 4.44
 (d, 1H), 4.64 (m, 1H), 7.10 (s, 1H), 7.24 (m, 3H), 7.36 (m, 1H), 8.58 (d, 1H), 12.36 (s, 1H);
 15 MS m/z 490, 492 [M + Na]⁺.

Example 25: 2,3-Dichloro-*N*-((1*R*,2*R*)-1-{[2-(dimethylamino)-2-oxoethyl]sulfonyl}-2,3-dihydro-1*H*-inden-2-yl)-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide



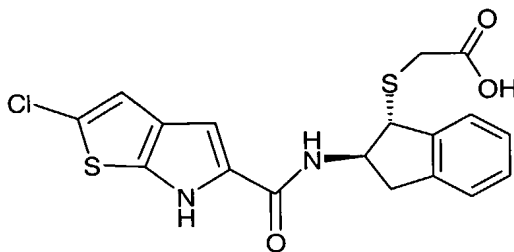
20 *m*-CPBA (70-75%, 150 mg, 0.61 mmol) was added to a solution of 2,3-dichloro-*N*-((1*R*,2*R*)-1-{[2-(dimethylamino)-2-oxoethyl]thio}-2,3-dihydro-1*H*-inden-2-yl)-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide (Example 24; 285 mg, 0.61 mmol) in DCM (7 mL) and the reaction
 was stirred at ambient temperature for 30 mins. A further portion of *m*-CPBA (75mg, 0.30
 mmol) was added and the reaction was stirred at ambient temperature for a further 1 h. The

reaction was quenched by addition of sat. aqueous NaHCO_3 (20 mL) and diluted with DCM (20 mL). The organic layer was separated, dried (MgSO_4), filtered and the volatiles removed *in vacuo*. Purification by column chromatography (eluent gradient: 1:2, EtOAc:hexanes to EtOAc) afforded the title compound (150 mg, 49%) as a white foam.

- 5 ^1H NMR (DMSO) δ : 2.77 (s, 3H), 3.05 (m, 4H), 3.31 (s, 3H), 3.52 (dd, 1H), 4.64 (d, 1H), 4.75 (d, 1H), 5.22 (m, 1H), 5.28 (s, 1H), 7.13 (s, 1H), 7.31 (m, 1H), 7.38 (m, 2H), 7.57 (d, 1H), 8.83 (d, 1H), 12.40 (s, 1H), MS m/z 522, 524 $[\text{M} + \text{Na}]^+$.

- 10 The following example was prepared by the method of **Example 23** using (+/-)-*trans*-methyl [(-2-{[(2-chloro-6*H*-thieno[2,3-*b*]pyrrol-5-yl)carbonyl]amino}-2,3-dihydro-1*H*-inden-1-yl)thio]acetate (**Intermediate 30**) as the methyl ester.

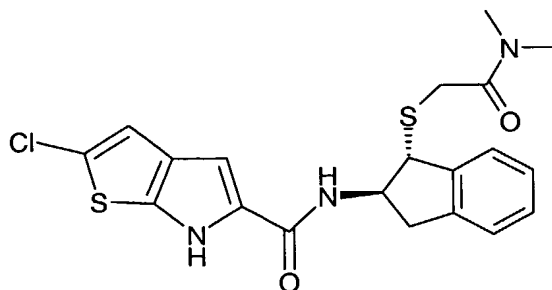
Example 26: (+/-)-*trans*-(-2-{[(2-Chloro-6*H*-thieno[2,3-*b*]pyrrol-5-yl)carbonyl]amino}-2,3-dihydro-1*H*-inden-1-yl)thio]acetic acid



15

^1H NMR δ : 3.00 (dd, 1H), 3.40 (m, 4H), 3.59 (d, 1H), 4.51 (s, 1H), 4.68 (m, 1H), 7.08 (s, 1H), 7.20 (s, 1H), 7.35 (m, 4H), 8.57 (d, 1H), 11.95 (s, 1H); MS m/z 429, 431 $[\text{M} + \text{Na}]^+$.

- 20 **Example 27: (+/-)-*trans*-2-Chloro-*N*-((1*R*,2*R*)-1-{[2-(dimethylamino)-2-oxoethyl]thio}-2,3-dihydro-1*H*-inden-2-yl)-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide**



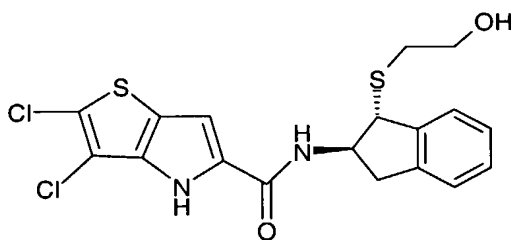
EDCI (32 mg, 0.169 mmol), HOBT (26 mg, 0.169 mmol) and dimethylamine (0.135 mL, 2.0M in THF, 0.270 mmol) was added to a solution of (+/-)-*trans*-(-2-{[(2-chloro-6*H*-thieno[2,3-*b*]pyrrol-5-yl)carbonyl]amino}-2,3-dihydro-1*H*-inden-1-yl)thio]acetic acid

(**Example 26**; 755 mg, 0.135 mmol), in THF (5 mL) and the mixture stirred at ambient temperature for 2 h. The reaction was diluted with EtOAc (50 mL) then extracted with 1M HCl (aqueous) (15 mL) then saturated aqueous NaHCO₃ (20 mL) and the organic layer was dried (MgSO₄), filtered and the volatiles removed *in vacuo*. Purification by column chromatography (eluent gradient: 1:1, EtOAc:hexanes to EtOAc) afforded the title compound (25 mg, 43 %) as a white solid.

¹H NMR δ: 2.80 (s, 3H), 2.95 (dd, 1H), 3.01 (s, 3H), 3.38 (dd, 1H), 2.67 (m, 2H), 4.43 (s, 1H), 4.68 (m, 1H), 7.02 (s, 1H), 7.15 (s, 1H), 7.28 (m, 3H), 7.34 (m, 1H), 8.53 (d, 1H), 11.87 (s, 1H); MS m/z 456, 458 [M+Na]⁺.

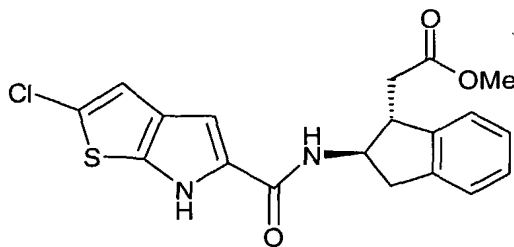
The following examples were prepared by the method of **Intermediate 29**, using either *tert*-butyl {(1*R*,2*R*)-1-[(2-hydroxyethyl)thio]-2,3-dihydro-1*H*-inden-2-yl} carbamate (**Intermediate 28**) or (+/-)-*trans*-methyl {-2-[(*tert*-butoxycarbonyl)amino]-2,3-dihydro-1*H*-inden-1-yl} acetate (**Intermediate 32**) as the carbamate and 2-Chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxylic acid (**Intermediate 4**) or 5-Carboxy-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole (**Intermediate 3**) as the carboxylic acid.

Example 28: 2,3-Dichloro-*N*-{(1*R*,2*R*)-1-[(2-hydroxyethyl)thio]-2,3-dihydro-1*H*-inden-2-yl}-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide



¹H NMR δ: 2.85 (m, 3H), 3.12 (m, 1H), 3.68 (dd, 1H), 3.90 (m, 2H), 4.45 (m, 1H), 4.86 (m, 1H), 6.30 (d, 1H), 6.62 (s, 1H), 7.27 (m, 3H), 7.38 (m, 1H), 9.52 (s, 1H); MS m/z 425, 427 [M + Na]⁺.

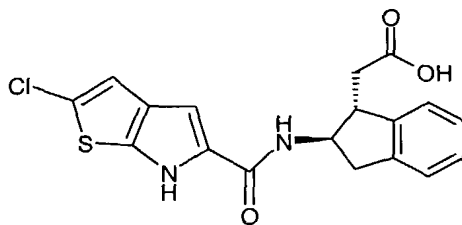
Example 29: (+/-)-trans-Methyl (-2-[[2-chloro-6H-thieno[2,3-b]pyrrol-5-yl)carbonyl]amino}-2,3-dihydro-1H-inden-1-yl)acetate



¹H NMR (DMSO) δ : 2.70 (d, 2H), 2.87 (dd, 1H), 3.20 (dd, 1H), 3.57 (s, 3H), 3.58 (m, 1H),
 5 4.42 (quin, 1H), 7.00 (s, 1H), 7.17 (m, 4H), 8.39 (d, 1H), 11.81 (s, 1H); MS m/z 389, 391
 [M]⁺.

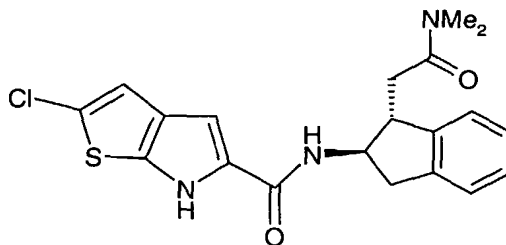
The following example was prepared by the method of **Example 23**, using (+/-)-trans-methyl-
 (-2-[[2-chloro-6H-thieno[2,3-b]pyrrol-5-yl)carbonyl]amino}-2,3-dihydro-1H-inden-1-
 10 yl)acetate (**Example 29**) as the ester.

Example 30: (+/-)-trans-(-2-[[2-Chloro-6H-thieno[2,3-b]pyrrol-5-yl)carbonyl]amino}-2,3-dihydro-1H-inden-1-yl)acetic acid



¹H NMR (DMSO) δ : 2.60 (m, 2H), 2.87 (dd, 1H), 3.20 (dd, 1H), 3.57 (m, 1H), 4.41 (quin,
 15 1H), 7.02 (d, 1H), 7.18 (m, 4H), 8.40 (d, 1H), 11.81 (s, 1H); MS m/z 375, 377 [M]⁺.

Example 31: (+/-)-trans-2-Chloro-N-{1-[2-(dimethylamino)-2-oxoethyl]-2,3-dihydro-1H-inden-2-yl}-6H-thieno[2,3-b]pyrrole-5-carboxamide



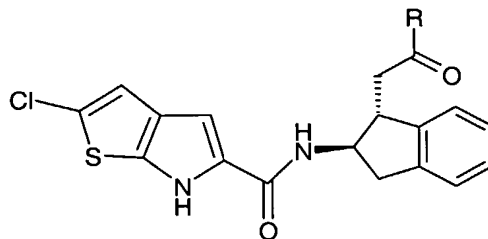
EDCI (64 mg, 0.33 mmol), HOBT (41 mg, 0.27 mmol) and dimethylamine (2.0M in THF, 0.20 mL, 0.40 mmol) was added to a solution of (+/-)-*trans*-(2-{[(2-chloro-6*H*-thieno[2,3-*b*]pyrrol-5-yl)carbonyl]amino}-2,3-dihydro-1*H*-inden-1-yl)acetic acid (Example 30; 100 mg, 0.27 mmol), in THF (6 mL) and the mixture was stirred at ambient temperature for 2 h. The reaction was diluted with EtOAc (50 mL) then extracted with 1M HCl (aq.) (15 mL), sat. aqueous NaHCO₃ (20 mL) and the organic layer was dried (MgSO₄), filtered and the volatiles removed *in vacuo*. Purification by column chromatography (eluent: 1:1, EtOAc:hexanes) afforded the title compound (69 mg, 64%) as a white solid.

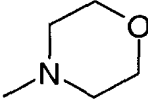
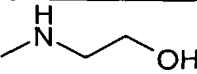
¹H NMR (DMSO) δ: 2.71 (m, 2H), 2.86 (s, 3H), 2.87 (m, 1H), 2.95 (s, 3H), 3.68 (m, 1H), 4.46 (quin, 1H), 7.03 (s, 1H), 7.18 (m, 5H), 8.45 (d, 1H), 11.81 (s, 1H); MS *m/z* 424, 426 [M + Na]⁺.

The following examples were made by method of **Example 31** using (+/-)-*trans*-(2-{[(2-chloro-6*H*-thieno[2,3-*b*]pyrrol-5-yl)carbonyl]amino}-2,3-dihydro-1*H*-inden-1-yl)acetic acid (**Example 30**) as the carboxylic acid and the appropriate commercially available amine.

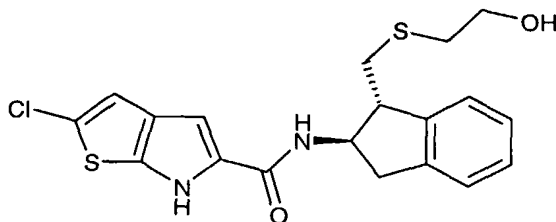
Example 32: (+/-)-*trans*-2-Chloro-*N*-[1-(2-morpholin-4-yl-2-oxoethyl)-2,3-dihydro-1*H*-inden-2-yl]-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide

Example 33: (+/-)-*trans*-2-Chloro-*N*-(1-{2-[(2-hydroxyethyl)amino]-2-oxoethyl}-2,3-dihydro-1*H*-inden-2-yl)-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide



Example	R	NMR (DMSO)	M/z
32		2.72 (m, 2H), 2.90 (dd, 1H), 3.26 (dd, 1H), 3.50 (m, 8H), 3.72 (q, 1H), 4.40 (quin, 1H), 7.02 (s, 1H), 7.22 (m, 5H), 8.43 (d, 1H), 11.81 (s, 1H).	444, 446
33		2.87 (m, 2H), 3.18 (m, 4H), 3.40 (m, 2H), 3.61 (m, 1H), 4.37 (m, 1H), 4.62 (m, 1H), 7.02 (s, 1H), 7.21 (m, 5H), 7.97 (m, 1H), 8.41 (d, 1H), 11.80 (s, 1H).	418, 420

Example 34: 2-Chloro-N-((1*R*,2*R*)-1-[(2-hydroxyethyl)thio]methyl)-2,3-dihydro-1*H*-inden-2-yl)-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide



5
 ((1*R*,2*R*)-2-{[(2-Chloro-6*H*-thieno[2,3-*b*]pyrrol-5-yl)carbonyl]amino}-2,3-dihydro-1*H*-inden-1-yl)methyl methanesulfonate (**Intermediate 19**; 424.5 mg, 1 mmol) in DMF (2 mL) was added to a solution of mercaptoethanol (0.42 mL, 6 mmol) and DBU (0.38 mL, 2.5 mmol) in DMF (4 mL) which had been heated at 60 °C for 10 minutes, heating was continued at 60 °C
 10 for 5 h, the reaction mixture was cooled, poured into saturated NaHCO₃ and the precipitate isolated by filtration. The resulting solid was taken up in EtOAc (30 mL) and water (15 mL), the organic layer was separated, washed with water (15 mL) and brine (15 mL) and dried (MgSO₄), filtered and evaporated. The residue was purified by column chromatography (EtOAc: hexane 1:9) to afford the title compound (170 mg, 42%).

15 ¹H NMR δ: 2.6 (t, 2H), 2.9 (m, 2H), 3.0 (dd, 1H), 3.3 (m, 1H), 3.4 (m, 1H), 3.5 (m, 2H), 4.5 (m, 1H), 4.7 (m, 1H), 7.0 (s, 1H), 7.1 (s, 1H), 7.2 (m, 3H), 7.4 (m, 1H), 8.4 (d, 1H), 11.8 (s, 1H); MS m/z 407.

The following examples were made by the process of **Example 34** using ((1*R*,2*R*)-2-{[(2-chloro-6*H*-thieno[2,3-*b*]pyrrol-5-yl)carbonyl]amino}-2,3-dihydro-1*H*-inden-1-yl)methyl

methanesulfonate (**Intermediate 19**) as the mesylate and the appropriate commercially known thiol.

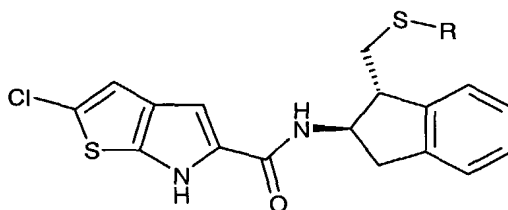
Example 35: 2-Chloro-N-((1R,2R)-1-[(3-hydroxypropyl)thio]methyl)-2,3-dihydro-1H-inden-2-yl)-6H-thieno[2,3-b]pyrrole-5-carboxamide

Example 36: 2-Chloro-N-((1R,2R)-1-[(2,3-dihydroxypropyl)thio]methyl)-2,3-dihydro-1H-inden-2-yl)-6H-thieno[2,3-b]pyrrole-5-carboxamide

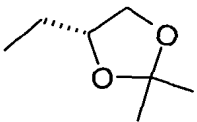
Example 37: N-[(1R,2R)-1-({[2-(Acetylamino)ethyl]thio}methyl)-2,3-dihydro-1H-inden-2-yl]-2-chloro-6H-thieno[2,3-b]pyrrole-5-carboxamide

Example 38: Methyl {[(1R,2R)-2-[(2-chloro-6H-thieno[2,3-b]pyrrol-5-yl)carbonyl]amino}-2,3-dihydro-1H-inden-1-yl)methyl]thio}acetate

Example 39: 2-Chloro-N-{(1R,2R)-1-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}thio)methyl)-2,3-dihydro-1H-inden-2-yl)-6H-thieno[2,3-b]pyrrole-5-carboxamide

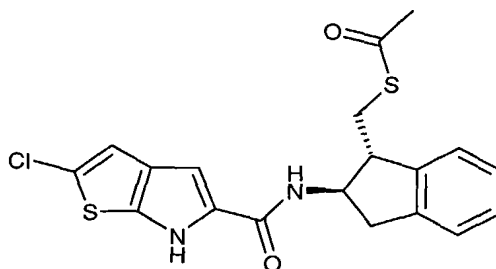


Example	R	NMR	M/z
35	-(CH ₂) ₃ OH	CDCl ₃ : 1.8 (m, 2H), 2.3 (s, 1H), 2.8 (m, 2H), 2.9 (m, 3H), 3.3 (m, 1H), 3.5 (m, 1H), 3.7 (m, 2H), 4.7 (m, 1H), 6.3 (d, 1H), 6.6 (s, 1H), 6.8 (s, 1H), 7.2 (m, 3H), 7.3 (m, 1H), 10.2 (s, 1H)	419 (M-H)
36		CDCl ₃ : 1.5-2.0 (br, 2H), 2.6-3.1 (m, 5H), 3.4-3.7 (m, 4H), 3.9 (m, 1H), 4.9 (m, 1H), 6.3 (m, 1H), 6.6 (s, 1H), 6.8 (s, 1H), 7.2 (m, 4H), 10.4 (d, 1H)	437
37	-(CH ₂) ₂ NAc	CDCl ₃ : 2.0(s, 3H), 2.7 (m, 2H), 2.9 (m, 3H), 3.5 (m, 4H), 4.8 (m, 1H), 6.3 (m, 1H), 6.8 (m, 2H), 6.9 (s, 1H), 7.2 (m, 3H), 7.4 (m, 1H), 10.2 (s, 1H)	448

38	-CH ₂ COOMe	CDCl ₃ : 2.9(dd, 1H), 3.0 (d, 1H), 3.1 (d, 1H), 3.3 (d, 2H), 3.5 (m, 1H), 3.6 (dd, 1H), 3.7 (s, 3H), 4.6 (m, 1H), 6.7 (m, 2H), 6.9 (s, 1H), 7.2 (m, 3H), 7.4 (m, 1H), 10.3 (s, 1H)	435
39		CDCl ₃ : 1.3 (s, 3H), 1.4 (s, 3H), 2.7 (m, 2H), 3.0 (m, 3H), 3.4 (q, 1H), 3.5 (dd, 1H), 3.7 (t, 1H), 4.1 (m, 1H), 4.2 (m, 1H), 4.7 (m, 1H), 6.4 (d, 1H), 6.6 (s, 1H), 6.8 (s, 1H), 7.2 (m, 4H), 10.4 (s, 1H)	499 (M+Na)

*Thiol prepared as described in *J. Chem. Soc.* **1967**, 1025.

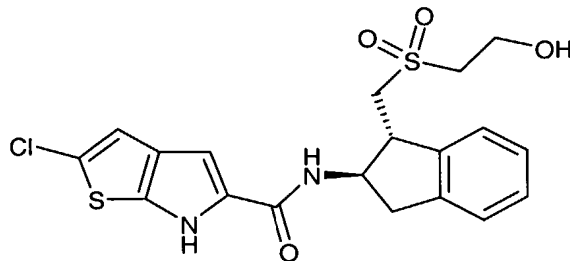
Example 40: *S*-[(((1*R*,2*R*)-2-[(2-Chloro-6*H*-thieno[2,3-*b*]pyrrol-5-yl)carbonyl]amino)-2,3-dihydro-1*H*-inden-1-yl)methyl] ethanethioate



((1*R*,2*R*)-2-[(2-Chloro-6*H*-thieno[2,3-*b*]pyrrol-5-yl)carbonyl]amino)-2,3-dihydro-1*H*-inden-1-yl)methyl methanesulfonate (**Intermediate 19**; 424.5 mg, 1 mmol) in DMF (2 mL) was added to a solution of thioacetic acid (91.2 mg, 1.2 mmol) and cesium carbonate (220 mg, 0.65 mmol) in DMF (10 mL). The solution was stirred for 16 hrs at ambient temperature then filtered. Water (15 mL) and EtOAc (50 mL) were added, the organic layer was separated, washed with water (2x20 mL) and brine (20 mL), dried (MgSO₄), filtered and evaporated. The residue was purified by column chromatography (EtOAc/CH₂Cl₂ 0-1%) to afford the title compound (200 mg, 50%).

¹H NMR (CDCl₃, 300MHz) δ: 2.3 (s, 3H), 2.9 (dd, 1H), 3.2 (m, 2H), 3.3 (m, 1H), 3.5(dd, 1H), 4.5(m, 1H), 6.5 (d, 1H), 6.7 (s, 1H), 6.9 (s, 1H), 7.2 (m, 3H), 7.3 (m, 1H), 10.2(s, 1H); MS m/z 404.

Example 41: 2-Chloro-*N*-((1*R*,2*R*)-1-[[2-hydroxyethyl)sulfonyl]methyl}-2,3-dihydro-1*H*-inden-2-yl)-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide



2-Chloro-*N*-((1*R*,2*R*)-1-[[2-hydroxyethyl)thio]methyl]-2,3-dihydro-1*H*-inden-2-yl)-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide (**Example 34**; 574 mg, 1.41 mmol) in THF (11 mL) was
 5 treated with *m*-CPBA (694 mg, 70-75%, 2.82 mmol) and the mixture was stirred at ambient temperature for 16 h before evaporated to dryness. Saturated NaHCO₃ (20 mL) and EtOAc (40 mL) were added and the organic layer was separated, washed with saturated NaHCO₃ (20 mL), water (20 mL) and brine (20 mL), dried (MgSO₄), filtered and evaporated to afford the
 10 title compound (473 mg, 76%) as a solid.

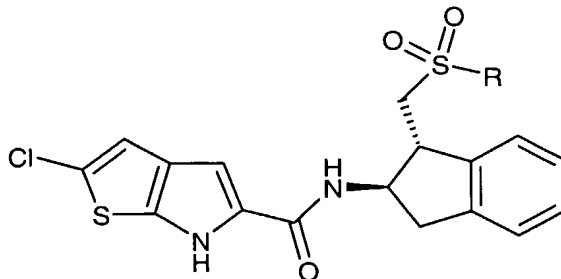
¹H NMR δ: 2.9 (dd, 1H), 3.2-3.4 (m, 3H), 3.6 (d, 2H), 3.8 (m, 3H), 4.6 (m, 1H), 5.2 (m, 1H), 7.0 (s, 1H), 7.1 (s, 1H), 7.2 (m, 3H), 7.5 (m, 1H), 8.4 (d, 1H), 11.8 (s, 1H); MS *m/z* 439 (M+H).

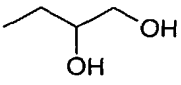
15 The following examples were made by the process of **Example 41**, using the appropriate thioether (**Example 35**, **Example 36** or **Example 37**).

Example 42: 2-Chloro-*N*-((1*R*,2*R*)-1-[[3-hydroxypropyl)sulfonyl]methyl}-2,3-dihydro-1*H*-inden-2-yl)-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide

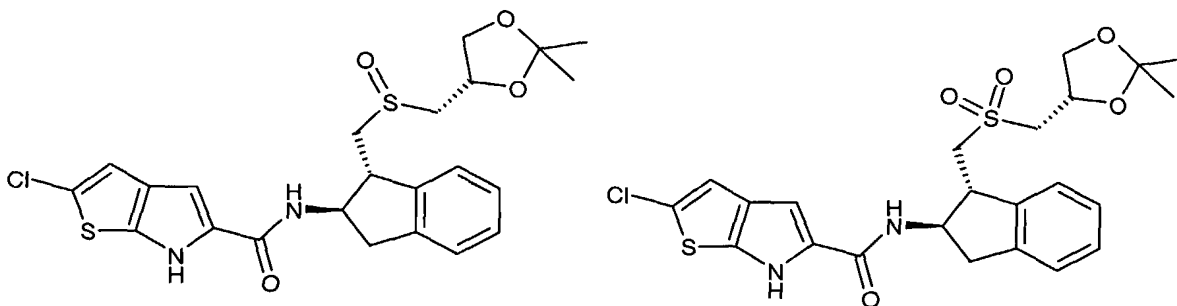
Example 43: 2-Chloro-*N*-((1*R*,2*R*)-1-[[2,3-dihydroxypropyl)sulfonyl]methyl}-2,3-dihydro-1*H*-inden-2-yl)-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide

Example 44: *N*-[(1*R*,2*R*)-1-([2-(Acetylamino)ethyl)sulfonyl]methyl]-2,3-dihydro-1*H*-inden-2-yl]-2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide



Example	Thioether	R	NMR	M/z
42	Example 35	-(CH ₂) ₃ OH	1.8 (m, 2H), 2.8 (m, 2H), 3.2 (m, 3H), 3.4 (q, 2H), 3.5 (m, 2H), 3.7 (m, 1H), 4.6 (m, 2H), 7.0 (s, 1H), 7.2 (s, 1H), 7.2 (m, 3H), 7.5 (m, 1H), 8.4 (d, 1H), 11.8 (s, 1H)	453
43	Example 36		2.9 (m, 1H), 3.1-3.4 (m, 5H), 3.6 (m, 2H), 3.8 (m, 1H), 4.0 (m, 1H), 4.6 (m, 1H), 4.8 (m, 1H), 5.3 (m, 1H), 7.0 (m, 1H), 7.1 (d, 1H), 7.2 (m, 3H), 7.5 (m, 1H), 8.4 (dd, 1H), 11.8 (s, 1H)	469
44	Example 37	-(CH ₂) ₂ NAC	1.9 (s, 3H), 3.0 (dd, 1H), 3.3-3.5 (m, 3H), 3.5 (m, 2H), 3.6 (d, 2H), 3.8 (m, 1H), 4.6 (m, 1H), 6.3 (m, 1H), 6.8 (m, 2H), 6.9 (s, 1H), 7.2 (m, 3H), 7.4 (m, 1H), 10.2 (s, 1H)	480

Example 45: 2-Chloro-N-((1R,2R)-1-(((4S)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)sulfinyl)methyl]-2,3-dihydro-1H-inden-2-yl)-6H-thieno[2,3-b]pyrrole-5-carboxamide and Example 46: 2-Chloro-N-((1R,2R)-1-(((4S)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)sulfonyl)methyl)-2,3-dihydro-1H-inden-2-yl)-6H-thieno[2,3-b]pyrrole-5-carboxamide



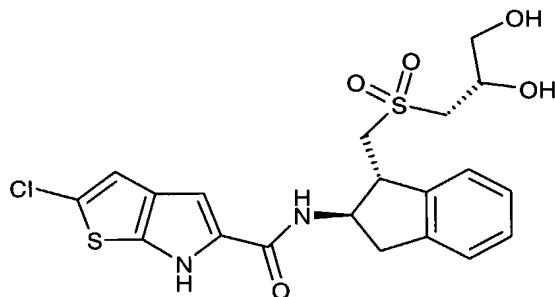
2-Chloro-N-((1R,2R)-1-(((4S)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)thio)methyl)-2,3-dihydro-1H-inden-2-yl)-6H-thieno[2,3-b]pyrrole-5-carboxamide (**Example 39**; 517 mg, 1.09

10 mmol) in DCM (20 mL) was treated with m-CPBA (496 mg, 70-75%, 1.6 mmol) in DCM (10 mL), the mixture was stirred at 0°C for 1 h, saturated NaHCO₃ (10 mL) and saturated sodium hydrogen sulphite (10 mL) were added and the mixture stirred for 10 mins. The organic layer

was separated, washed with water (10 mL) and brine (10 mL), dried (MgSO₄), filtered and evaporated. The residue was purified by column chromatography (eluent gradient: 30-100% EtOAc in DCM) to afford 2-chloro-*N*-{(1*R*,2*R*)-1-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl)sulfonyl)methyl]-2,3-dihydro-1*H*-inden-2-yl}-6*H*-thieno[2,3-*b*]pyrrole-5-

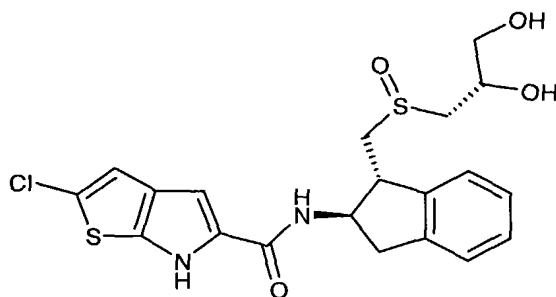
- 5 carboxamide (271 mg); ¹H NMR (CDCl₃) δ: 1.3 (s, 3H), 1.4 (s, 3H), 2.9 (dd, 1H), 3.0 (dd, 1H), 3.4-3.7 (m, 3H), 3.75 (dd, 1H), 3.8-4.0 (m, 2H), 4.2 (m, 1H), 4.7 (m, 2H), 6.7 (s, 1H), 6.9 (m, 2H), 7.2 (m, 4H), 10.1 (s, 1H); MS m/z: 509 (M+H) and 2-Chloro-*N*-{(1*R*,2*R*)-1-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl)sulfinyl)methyl]-2,3-dihydro-1*H*-inden-2-yl}-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide (131 mg); HPLC RT 2.31 mins (HPLC specification:
10 Waters 2790 Separations module, Column: Phenomenex Synergi 4u MAX-RP 8A (50x2 mm), Mobile phase: Acetonitrile:Water:Formic acid, 49.5:49.5:1, Flow rate/operating pressure: 1.1ml/min at 200psi); MS m/z: 493 (M+H).

Example 47: 2-Chloro-*N*-[(1*R*,2*R*)-1-[(*S*)-2,3-dihydroxypropyl)sulfonyl)methyl]-2,3-dihydro-1*H*-inden-2-yl]-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide



- 2-Chloro-*N*-{(1*R*,2*R*)-1-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl)sulfonyl)methyl]-2,3-dihydro-1*H*-inden-2-yl}-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide (**Example 46**; 271 mg, 0.53 mmol) was stirred at 60 °C for 2 h with a mixture of acetic acid (5 mL) and water (1 mL). The
20 solvent was evaporated to afford the title compound as a white solid (222 mg, 89%). ¹H NMR δ: 2.9 (dd, 1H), 3.1-3.4 (m, 5H), 3.6 (d, 2H), 3.8 (m, 1H), 4.0 (m, 1H), 4.6 (m, 1H), 4.8 (m, 1H), 5.3 (m, 1H), 7.0 (s, 1H), 7.1 (s, 1H), 7.2 (m, 3H), 7.5 (m, 1H), 8.4 (d, 1H), 11.8 (s, 1H); MS m/z 469.

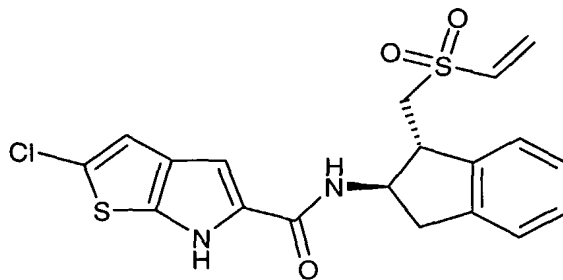
Example 48: 2-Chloro-*N*-[(1*R*,2*R*)-1-([(2*S*)-2,3-dihydroxypropyl]sulfinyl)methyl]-2,3-dihydro-1*H*-inden-2-yl]-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide



2-Chloro-*N*-{[(1*R*,2*R*)-1-([(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl)sulfinyl]methyl}-2,3-dihydro-1*H*-inden-2-yl]-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide (**Example 45**; 131 mg, 0.27mmol) was stirred for 2 h at 60°C with a mixture of acetic acid (5 mL) and water (1 mL). The solvent was evaporated to afford the title compound as a white solid (80 mg, 67%).

¹H NMR δ: 3.0 (m, 5H), 3.3-3.4 (m, 3H), 3.7 (m, 1H), 3.9 (m, 1H), 4.5 (m, 1H), 4.7 (m, 1H), 5.1 (m, 1H), 7.0 (s, 1H), 7.1 (s, 1H), 7.2 (m, 3H), 7.4(m, 1H), 8.5(m, 1H), 11.8 (s, 1H); MS *m/z* 453.

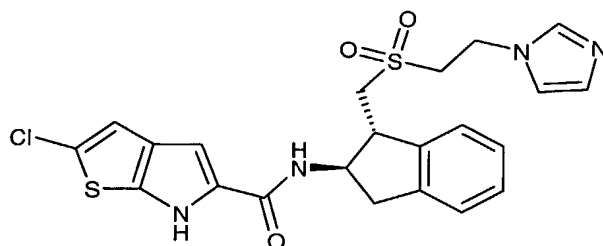
Example 49: 2-Chloro-*N*-[(1*R*,2*R*)-1-[(ethenylsulfonyl)methyl]-2,3-dihydro-1*H*-inden-2-yl]-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide



2-Chloro-*N*-{[(1*R*,2*R*)-1-[(2-hydroxyethyl)sulfonyl]methyl}-2,3-dihydro-1*H*-inden-2-yl]-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide (**Example 41**; 385 mg, 0.879 mmol) in THF (7 mL) was treated first with triethylamine (0.257 mL, 1.87 mmol) then by the dropwise addition of mesyl chloride (0.071 mL, 0.923 mmol) at 0 °C and the resultant solution was allowed to warm to ambient temperature and stirred for 16 h. The mixture was filtered and the filtrate evaporated to dryness. Water (15 mL) and EtOAc (30 mL) were added and the organic layer was separated, washed with water (15 mL) and brine (15 mL) and the organic layer was dried (MgSO₄), filtered and evaporated. The residue was purified by column chromatography (EtOAc:toluene, 1:9) to afford the title compound (175 mg, 45%).

¹H NMR (CDCl₃) δ: 3.0 (dd, 1H), 3.4(dd, 1H), 3.5 (d, 1H), 3.6(d, 1H), 3.9 (m, 1H), 4.6 (m, 1H), 6.2 (1H, d), 6.5 (d, 1H), 6.7-6.9 (m, 4H), 7.2 (m, 3H), 7.3 (m, 1H), 10.2 (s, 1H) ; MS m/z 421.

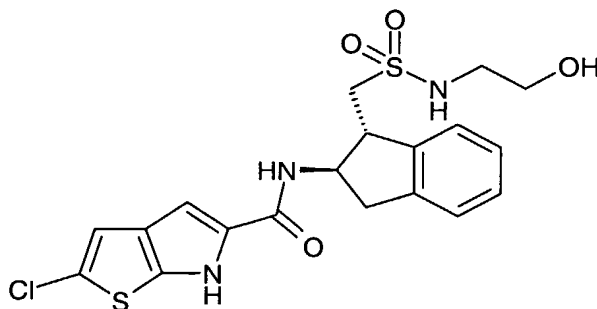
5 **Example 50: 2-Chloro-*N*-[(1*R*,2*R*)-1-({[2-(1*H*-imidazol-1-yl)ethyl]sulfonyl)methyl]-2,3-dihydro-1*H*-inden-2-yl]-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide**



2-Chloro-*N*-[(1*R*,2*R*)-1-[(ethenylsulfonyl)methyl]-2,3-dihydro-1*H*-inden-2-yl]- 6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide (**Example 49**; 80 mg, 0.19 mmol) was dissolved in methanol (5 mL) and stirred with imidazole (129 mg, 1.9 mmol) at ambient temperature for 24 h. The resultant white solid was isolated by filtration, stirred with EtOAc for 15 mins, isolated by filtration and dried under vacuum over phosphorous pentoxide (P₂O₅) to afford the title compound (70 mg, 75%) as a solid.

¹H NMR δ: 2.9 (dd, 1H), 3.3(dd, 1H), 3.5 (m, 2H), 3.8(m, 3H), 4.4(m, 2H), 4.6 (m, 1H), 6.8 (s, 1H), 6.9 (m, 4H), 7.0 (s, 1H), 7.15 (s, 1H), 7.2 (m, 3H), 7.4 (m, 1H), 7.7(s, 1H), 8.4 (d, 1H), 11.8 (s, 1H); MS m/z 489.

Example 51: 2-Chloro-*N*-[(1*R*,2*R*)-1-({[2-(2-hydroxyethyl)amino]sulfonyl)methyl]-2,3-dihydro-1*H*-inden-2-yl]-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide



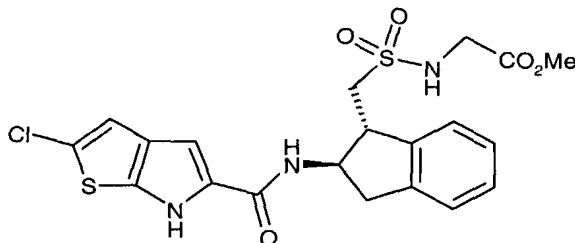
Triethylamine (0.12 mL, 0.87 mmol), HOBT (30 mg, 0.22 mmol), 1-[(1*R*,2*R*)-2-amino-2,3-dihydro-1*H*-inden-1-yl]-*N*-(2-hydroxyethyl)methanesulfonamide hydrochloride (**Intermediate 33**, 61 mg, 0.20 mmol) and EDCI (42 mg, 0.22 mmol) were added to a suspension of 2-

chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxylic acid (**Intermediate 4**; 32 mg, 0.16 mmol) in DMF (5 mL). The reaction was stirred at ambient temperature for approximately 16 h. The reaction mixture was diluted with water (10 mL) and washed with EtOAc (20 mL). The organic layer was washed with water (2x10 mL), 1M citric acid (10 mL), saturated sodium bicarbonate solution (10 mL) and evaporated to give the title compound (38 mg, 42%) as a cream solid.

¹H NMR δ: 2.96 (m, 3H), 3.33 (m, 5H), 3.63 (m, 1H), 4.56 (m, 1H), 4.71 (t, 1H), 7.03 (s, 1H), 7.14 (s, 1H), 7.21 (m, 4H), 7.51 (m, 1H), 8.46 (d, 1H), 11.86 (s, 1H); MS m/z 454.1.

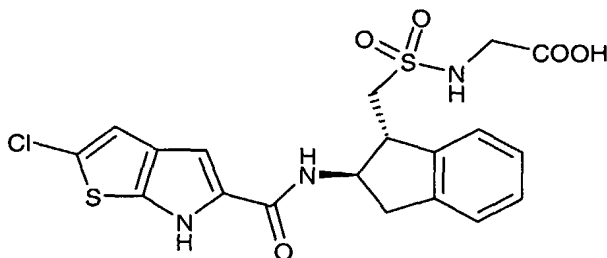
- 10 The following example was made by the process used in **Example 51** using 2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxylic acid (**Intermediate 4**) as the carboxylic acid and methyl *N*-([[(1*R*,2*R*)-2-amino-2,3-dihydro-1*H*-inden-1-yl]methyl]sulfonyl)glycinate (**Intermediate 34**) as the amine.

15 **Example 52: Methyl *N*-{[[(1*R*,2*R*)-2-{[1-(2-chloro-6*H*-thieno[2,3-*b*]pyrrol-5-yl)vinyl]amino}-2,3-dihydro-1*H*-inden-1-yl)methyl]sulfonyl}glycinate**



¹H-NMR (CDCl₃) δ: 2.9 (dd, 1H), 3.4 (m, 2H), 3.6 (dd, 1H), 3.8 (s, 3H), 3.9 (m, 1H), 4.1 (s, 2H), 5.1 (m, 1H), 6.5 (d, 1H), 6.6 (s, 1H), 6.8 (s, 1H), 7.2 (m, 3H), 7.3(m, 1H), 9.0-10.0 (br, 1H); MS m/z 482.

Example 53: *N*-{[[(1*R*,2*R*)-2-{[1-(2-Chloro-6*H*-thieno[2,3-*b*]pyrrol-5-yl)vinyl]amino}-2,3-dihydro-1*H*-inden-1-yl)methyl]sulfonyl}glycine



Methyl *N*-{[(((1*R*,2*R*)-2-{[1-(2-chloro-6*H*-thieno[2,3-*b*]pyrrol-5-yl)vinyl]amino}-2,3-dihydro-1*H*-inden-1-yl)methyl]sulfonyl}glycinate (**Example 52**; 10 mg, 0.02 mmol) in THF:MeOH (3:1, 0.4 mL) was treated with 1N lithium hydroxide (0.04 mL, 0.04 mmol) and the solution was stirred at ambient temperature for 2 h, then evaporated to dryness and acidified with 1N hydrochloric acid. The resultant solid was isolated by filtration, washed with water and dried over phosphorous pentoxide (P₂O₅) to give the title compound (8.3 mg, 86%) as a white solid. ¹H NMR δ: 2.9 (dd, 1H), 3.3 (dd, 1H), 3.5 (m, 2H), 3.7 (m, 1H), 3.8 (s, 2H), 4.6 (m, 1H), 7.0 (s, 1H), 7.1 (s, 1H), 7.2 (m, 4H), 7.7(m, 2H), 8.7 (m, 2H), 11.5-13.0 (br, 1H); MS *m/z* 468 (M+H).

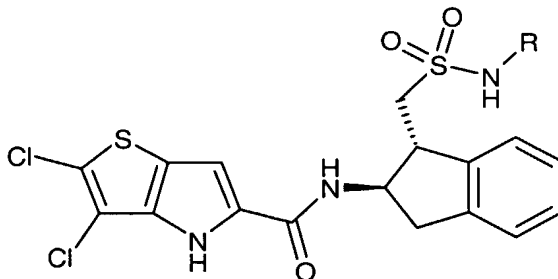
The following examples were made by the process used for **Example 52** using 2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylic acid (**Intermediate 3**) as the acid and the appropriate amine (**Intermediates 35 to 38**):

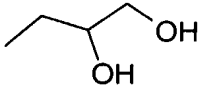
Example 54: 2,3-Dichloro-*N*-[(1*R*,2*R*)-1-([(2-hydroxyethyl)amino]sulfonyl)methyl]-2,3-dihydro-1*H*-inden-2-yl]-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide

Example 55: 2,3-Dichloro-*N*-((1*R*,2*R*)-1-[(propylamino)sulfonyl]methyl)-2,3-dihydro-1*H*-inden-2-yl)-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide

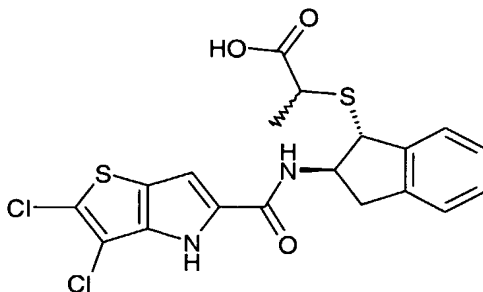
Example 56: 2,3-Dichloro-*N*-{(1*R*,2*R*)-1-[(morpholin-4-ylsulfonyl)methyl]-2,3-dihydro-1*H*-inden-2-yl}-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide

Example 57: 2,3-Dichloro-*N*-[(1*R*,2*R*)-1-([(2,3-dihydroxypropyl)amino]sulfonyl)methyl]-2,3-dihydro-1*H*-inden-2-yl]-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide



Example	Amine	R	NMR	M/z
54	Intermediate 35	$-(\text{CH}_2)_2\text{OH}$	2.9 (dd, 1H), 3.0 (t, 2H), 3.3 (m, 2H), 3.4 (m, 3H), 3.6 (m, 1H), 4.8 (q, 1H), 4.9 (m, 1H), 7.1 (s, 1H), 7.2 (m, 4H), 7.4 (m, 1H), 8.5 (d, 1H), 12.3 (s, 1H)	488
55	Intermediate 36	$-(\text{CH}_2)_2\text{CH}_3$	0.9 (t, 3H), 1.4 (q, 2H), 2.8 (m, 2H), 2.9 (dd, 1H), 3.2 (m, 2H), 3.5 (dd, 1H), 3.6 (m, 1H), 4.8 (d, 1H), 7.2 (m, 4H), 7.5 (m, 1H), 8.6 (d, 1H), 12.4 (s, 1H)	486
56	Intermediate 37	$-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2-$	3.0 (dd, 1H), 3.2 (t, 4H), 3.3 (m, 1H), 3.5 (dd, 1H), 3.6 (q, 1H), 3.65 (t, 4H), 3.8 (m, 1H), 4.7 (m, 1H), 7.2 (s, 1H), 7.3 (m, 3H), 7.6 (m, 1H), 8.6 (m, 1H), 12.4 (s, 1H)	514
57	Intermediate 38		2.9 (m, 2H), 3.1 (m, 1H), 3.4 (m, 4H), 3.5 (m, 1H), 3.7 (m, 1H), 4.5 (m, 1H), 4.6 (m, 1H), 4.8 (m, 1H), 7.1 (m, 2H), 7.2 (m, 3H), 7.5 (m, 1H), 8.5 (d, 1H), 12.3 (s, 1H)	518

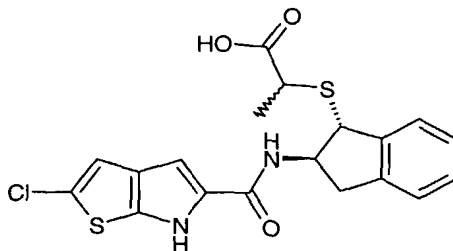
Example 58: (2R/S)-[(((1R,2R)-2-[(2,3-Dichloro-4H-thieno[3,2-b]pyrrol-5-yl)carbonyl]amino}-2,3-dihydro-1H-inden-1-yl)thio]propanoic acid



- 5 This Example was made from Intermediate 52 by an analogous process to that used for Example 23.

¹H NMR δ: 1.39 (dd, 3H), 2.94 (dt, 1H), 3.43 (m, 1H), 3.85 (m, 1H), 4.58 (m, 2H), 7.12 (s, 1H), 7.26 (m, 4H), 8.57 (dd, 1H), 12.38 (s, 1H), 12.52 (s, 1H); MS m/z 455.1.

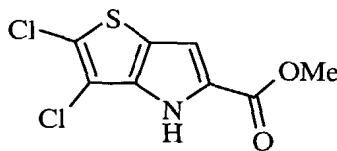
Example 59: (2*R/S*)-[(((1*R,2R*)-2-[[2-Chloro-6*H*-thieno[2,3-*b*]pyrrol-5-yl)carbonyl]amino}-2,3-dihydro-1*H*-inden-1-yl)thio]propanoic acid



This Example was made from Intermediate 53 by an analogous process to that used for Example 23.

¹H NMR δ: 1.39 (dd, 3H), 2.94 (dt, 1H), 3.43 (m, 1H), 3.85 (m, 1H), 4.58 (m, 2H), 7.01 (s, 1H), 7.12 (s, 1H), 7.26 (m, 4H), 8.51 (dd, 1H), 11.90 (s, 1H), 12.53 (s, 1H); MS m/z 421.2.

Intermediate 1: 2,3-Dichloro-5-methoxycarbonyl-4*H*-thieno[3,2-*b*]pyrrole



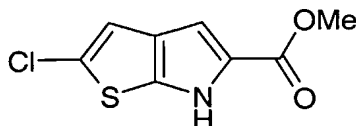
15

Methanolic sodium methoxide solution (5 mL, 28% w/v solution, 25.9 mmol) was diluted with MeOH (10 ml) and was cooled to -25 °C under nitrogen. A solution of 3,4-dichloro-5-carbonyl-4*H*-thieno[3,2,*b*]pyrrole (DE 2814798; 1.2 g, 6.63 mmol) and methyl azidoacetate (3.0 g, 26.09 mmol) in MeOH (15 ml) was added dropwise, maintaining the temperature at -25°C. On completion of addition the solution was allowed to warm to 5°C over a period of approximately 16 hours. The solution was added to saturated aqueous ammonium chloride (250 ml) and the mixture was extracted using dichloromethane. The combined organic layers were concentrated at ambient temperature. The residue was taken up in xylene (30 ml) and this solution was added dropwise to xylene (120 ml) under reflux. The solution was heated under reflux for 30 minutes before being cooled and concentrated. The

title compound was purified by crystallisation (EtOAc/isohexane) to afford the title compound (1.08 g, 65%) as a solid.

^1H NMR (CDCl_3) δ : 9.2 (1H, br), 7.0 (1H, s), 3.9 (3H, s); m/z 248.2.

5 **Intermediate 2: 2-Chloro-5-methoxycarbonyl-6H-thieno[2,3-b]pyrrole**

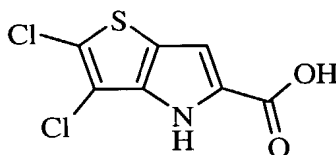


This was made using an analogous procedure to Intermediate 1 starting from the corresponding aldehyde (Gronowitz *et al.* Tetrahedron, Vol.32, 1976, p.1403).

^1H NMR (CDCl_3) δ : 9.4-9.2 (1H, br), 7.0 (1H, s), 6.9 (1H, s), 3.9 (3H, s); m/z 214

10

Intermediate 3: 5-Carboxy-2,3-dichloro-4H-thieno[3,2-b]pyrrole

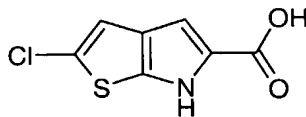


2,3-Dichloro-5-methoxycarbonyl-4H-thieno[3,2-b]pyrrole (**Intermediate 1**; 1.22 g, 5.66 mmol) was taken up in MeOH (10 ml) and was heated under reflux. Aqueous lithium

15 hydroxide (3.0 ml, 2.0 M, 6.0 mmol) was added portionwise over 45 minutes. The mixture was heated under reflux for 1 hour before being cooled and concentrated. Water (15 ml) was added and the solution was neutralised using aqueous hydrochloric acid (5.66 mL, 2.0 M, 3.0 ml). The solution was extracted using EtOAc, and the combined organic layers were concentrated to afford the title compound (1.18 g, 100%) as a yellow solid

20 ^1H NMR (CDCl_3) δ : 7.0 (1H, s); m/z 234.2.

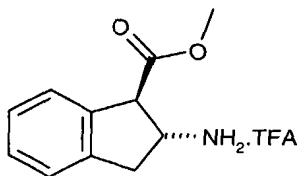
Intermediate 4: 5-Carboxy-2-chloro-6H-thieno[2,3-b]pyrrole



This was made using an analogous method to Intermediate 3, using 2-Chloro-5-methoxycarbonyl-6H-thieno[2,3-b]pyrrole (**Intermediate 2**) as the starting material.

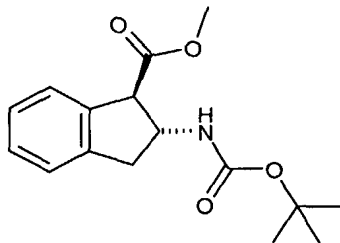
25

^1H NMR (CDCl_3) δ : 12.6-12.7 (1H, b), 12.0-12.1 (1H, b), 7.15 (1H, s), 6.9 (1H, s); m/z 183.

Intermediate 5: Methyl (1R,2R)-2-aminoindane-1-carboxylate trifluoroacetic acid salt

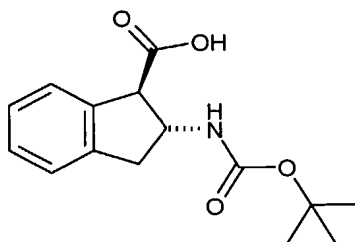
Methyl (1R, 2R)-2-[(*tert*-butoxycarbonyl)amino]indane-1-carboxylate (**Intermediate 6**; 1.3g, 4.43 mmol) was dissolved in DCM (5 mL), TFA (5 mL) added and the mixture stirred at ambient temperature for 4 h. The volatiles were removed under reduced pressure to give the title compound (1.35 g, 100%) as a foam.

¹H NMR (CDCl₃) δ: 3.1(dd, 1H), 3.45(dd, 1H), 3.74(s, 3H), 4.27(d, 1H), 4.4(m, 1H), 7.3(m, 1H).

Intermediate 6: Methyl (1R,2R)-2-[(*tert*-butoxycarbonyl)amino]indane-1-carboxylate

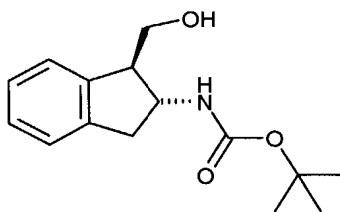
(1R,2R)-2-[(*tert*-Butoxycarbonyl)amino]indane-1-carboxylic acid (**Intermediate 7**; 1.85 g, 6.65 mmol) was dissolved in methanol (25 mL) and *isohexane* (25 mL), trimethylsilyldiazomethane (7.0 mL, 2.0M in hexane, 1.4 mmol) was added and the mixture stirred at ambient temperature for 24 h. The volatiles were removed by evaporation and the crude residue purified by silica gel chromatography (8:1, *iso*-hexane:ethyl acetate) to give the title compound (1.3 g, 68%) as a foam.

¹H NMR (CDCl₃) δ: 1.42(s, 9H), 2.81(dd, 1H), 3.48(dd, 1H), 3.75(s, 3H), 3.97(d, 1H), 4.75(m, 2H), 7.25(m, 4H).

Intermediate 7: (1R,2R)-2-[(*tert*-Butoxycarbonyl)amino]indane-1-carboxylic acid

To a solution of *tert*-butyl [(1R,2R)-1-(hydroxymethyl)-2,3-dihydro-1*H*-inden-2-yl]carbamate (**Intermediate 8**; 1.75 g, 6.65 mmol) in CCl₄ (20 mL) and CH₃CN (20 mL) was added sodium metaperiodate (5.7 g, 26.6 mmol) in water (30 mL) and ruthenium trichloride hydrate (138 mg, 0.665 mmol) and the mixture stirred at ambient temperature for 3 h. Ethyl acetate (100 mL) was added, the organic phase separated, washed with water (2 x 10 mL), brine (25 mL), dried (MgSO₄), filtered and the volatiles removed under reduced pressure to give the title compound (1.9 g, 100%) as a brown foam.

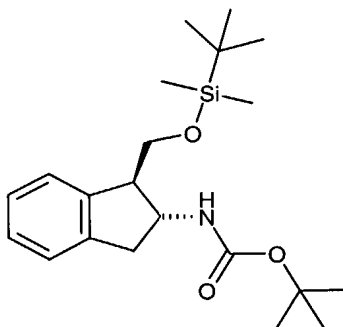
¹H NMR δ: 1.39 (s, 9H), 2.78 (dd, 1H), 3.02 (dd, 1H), 3.85 (d, 1H), 4.5 (m, 1H), 7.2 (m, 4H).

Intermediate 8: *tert*-Butyl [(1R,2R)-1-(hydroxymethyl)-2,3-dihydro-1*H*-inden-2-yl]carbamate

Tetrabutylammonium fluoride (10.0 mL, 2.0M in THF, 20.0 mmol) was added to a solution of *tert*-butyl [(1R,2R)-1-({[*tert*-butyl(dimethyl)silyl]oxy)methyl}-2,3-dihydro-1*H*-inden-2-yl]carbamate (**Intermediate 9**; 4.1 g, 10.9 mmol) in THF (50 mL) and stirred at ambient temperature for 4 h. The volatiles were removed under reduced pressure and the residue dissolved in ethyl acetate (100 mL), washed with water (2 x 50 mL), brine (50 mL), dried (MgSO₄) and the volatiles removed under reduced pressure. The crude residue was triturated (4:1, iso-hexane:ethyl acetate), filtered and dried to give the title compound (1.5 g, 54%) as white solid.

¹H NMR δ: 1.44 (s, 9H), 2.78 (dd, 1H), 3.15 (m, 2H), 3.61 (m, 1H), 3.75 (m, 1H), 4.07 (m, 1H), 4.7 (m, 1H), 7.19 (m, 4H), 7.37 (m, 1H).

Intermediate 9: *tert*-Butyl [(1*R*,2*R*)-1-([*tert*-butyl(dimethyl)silyl]oxy)methyl)-2,3-dihydro-1*H*-inden-2-yl]carbamate

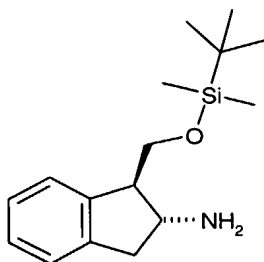


(1*R*,2*R*)-1-([*tert*-Butyl(dimethyl)silyl]oxy)methyl)-2,3-dihydro-1*H*-inden-2-yl]amine

- 5 **(Intermediate 10;** 3.1 g, 11.2 mmol) and triethylamine (3.1 mL, 22.4 mmol) were dissolved in DCM (40 mL). Di-*tert*-butyl dicarbonate (2.9 g, 13.4 mmol) in DCM (10 mL) was added and the mixture stirred at ambient temperature for 24 h. The volatiles were removed under reduced pressure and the residue dissolved in ethyl acetate (75 mL), washed with water (2 x 50 mL), brine (50 mL), dried (MgSO₄) and the volatiles removed under reduced pressure. The
- 10 crude residue was purified by silica gel chromatography (16:1, iso-hexane:ethyl acetate) to give the title compound (4.2 g, 100%) as a colourless oil.

¹H NMR δ: 0.3 (d, 6H), 0.85 (s, 9H), 1.42 (s, 9H), 2.75 (dd, 1H), 3.15 (m, 2H), 3.79 (m, 1H), 3.95 (m, 1H), 4.05 (m, 1H), 7.15 (m, 4H), 7.3 (m, 1H).

- 15 **Intermediate 10: [(1*R*,2*R*)-1-([*tert*-Butyl(dimethyl)silyl]oxy)methyl)-2,3-dihydro-1*H*-inden-2-yl]amine**



(1*S*,2*S*)-1-([*tert*-Butyl(dimethyl)silyl]oxy)methyl)-2,3-dihydro-1*H*-inden-2-yl

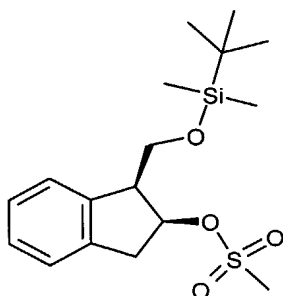
- methanesulfonate (**Intermediate 11;** 7.2g, 20.2 mmol) was dissolved in DMA (50 mL),
- 20 sodium azide (3.94 g, 60.6 mmol) added and the mixture stirred at 60 °C for 7 h. The mixture was poured into ethyl acetate (250 mL), washed with water (6 x 75 mL), brine (100 mL) and dried (MgSO₄). Palladium on carbon (500 mg, 10% w/w) was added, the mixture stirred

under a hydrogen atmosphere for 6h, filtered through Celite and the volatiles removed under reduced pressure to give the title compound (5.2 g, 93%) as a pale brown oil.

$^1\text{H NMR } \delta$: 0.07 (d, 6H), 0.9 (s, 9H), 2.58 (dd, 1H), 2.89 (m, 1H), 3.1 (dd, 1H), 3.3 (broad s, 2H), 3.41 (m, 1H), 3.85 (m, 2H), 7.2 (m, 4H).

5

Intermediate 11: (1S,2S)-1-([*tert*-Butyl(dimethyl)silyl]oxy)methyl)-2,3-dihydro-1H-inden-2-yl methanesulfonate



(1S,2S)-1-([*tert*-Butyl(dimethyl)silyl]oxy)methyl)indan-2-ol (**Intermediate 12**; 6.3 g, 22.65

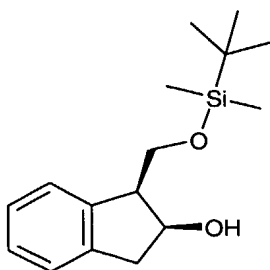
10 mmol) and triethylamine (4.7 mL, 34.0 mmol) were dissolved in DCM (90 mL) at 5 °C.

Methanesulfonyl chloride (2.86 g, 24.9 mmol) in DCM (10 mL) was added and the mixture stirred at ambient temperature for 2h. The volatiles were removed under reduced pressure and the residue dissolved in ethyl acetate (150 mL), washed with water (2x50 mL), brine (50 mL),

15 dried (MgSO_4) and the volatiles removed under reduced pressure. The crude residue was purified by silica gel chromatography (6:1, iso-hexane:ethyl acetate) to give the title compound (7.2 g, 89%) as a colourless oil.

$^1\text{H NMR } \delta$: 0.03 (d, 6H), 0.85 (s, 9H), 3.19 (s, 3H), 3.21 (m, 2H), 3.45 (m, 1H), 3.95 (m, 2H), 5.45 (m, 1H), 7.22 (m, 4H).

20 **Intermediate 12: (1S,2S)-1-([*tert*-Butyl(dimethyl)silyl]oxy)methyl)indan-2-ol**

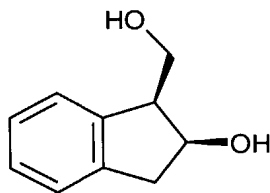


(1R,2S)-1-(Hydroxymethyl)-1,3-dihydro-2H-inden-2-one (**Intermediate 13**; 9.0 g, 54.8 mmol) and imidazole (4.5 g, 65.8 mmol) were dissolved in DCM (75 mL) at 10 °C. *tert*-

Butyldimethylchlorosilane (9.1 g, 60.3 mmol) in DCM (25 mL) was added, the mixture allowed to warm to ambient temperature and stirred for 2 h. The volatiles were removed under reduced pressure and the residue dissolved in ethyl acetate (150 mL), washed with water (2 x 50 mL), brine (50 mL), dried (MgSO₄) and the volatiles removed under reduced pressure. The crude residue was purified by silica gel chromatography (16:1, iso-hexane:ethyl acetate) to give the title compound (9.5 g, 62%) as a colourless oil.

¹H NMR δ: 0.03(d, 6H), 0.9(s, 9H), 2.78(dd, 1H), 3.0(dd, 1H), 3.1(m, 1H), 3.9(m, 2H), 4.54(m, 1H), 4.68(d, 1H), 7.2(m, 4H).

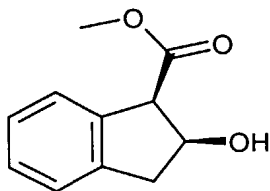
10 **Intermediate 13: (1R,2S)-1-(Hydroxymethyl)-1,3-dihydro-2H-inden-2-one**



Methyl (1R,2S)-2-hydroxyindane-1-carboxylate (**Intermediate 14**; 10.56 g, 55.0 mmol) was dissolved in dry THF (100 mL) under a nitrogen atmosphere at 0 °C. LiBH₄ (55.0 mL, 2.0M in THF, 110.0 mmol) was added and the reaction stirred between 0 to 5 °C for 0.5 h, allowed to warm to ambient temperature and stirred for a further 2h. The mixture was poured into saturated NaHCO₃, extracted with ethyl acetate (200 mL) and the organic phase washed with water (2 x 50 mL), brine (50 mL) and dried (MgSO₄). The volatiles were removed by evaporation under reduced pressure to give the title compound (9.1g, 93%) as a colourless oil.

¹H NMR δ: 2.7 (m, 1H), 2.95 (m, 1H), 3.05 (m, 1H), 3.55 (m, 1H), 3.8 (m, 1H), 4.55 (m, 3H), 7.2 (m, 4H).

Intermediate 14: Methyl (1R,2S)-2-hydroxyindane-1-carboxylate



(Reference:Didier, E *et al* Tetrahedron 47(27), 4941-4958, 1991)

25 De-ionised water (20 L) was warmed to 34°C, bakers yeast (3 Kg) added and the mixture stirred for 0.5hr. Methyl 2-oxoindane-1-carboxylate (40g, 0.21 mmol) was added, the

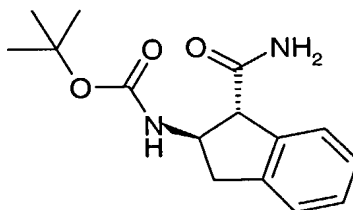
suspension stirred for 3 days and filtered through Celite. The aqueous filtrate was extracted with ethyl acetate (4 x 2.5L) and the organic extracts dried (MgSO₄), filtered and the volatiles removed by evaporation under reduced pressure. The crude residues were purified by flash silica gel chromatography (4:1 iso-hexane:ethyl acetate) the solvent evaporated and the resultant solid recrystallised from iso-hexane/ethyl acetate to give the title compound (10.8 g, 27%) as colourless needles.

Mp = 72.5-73.5°C (lit = 73.2°C)

[α]_D = +48.7° (C=1.0, CHCl₃) (lit = +48.3°)

¹H NMR δ : 2.85 (dd, 1H), 3.04 (dd, 1H), 3.61 (s, 3H), 4.1 (d, 1H), 4.76 (m, 1H), 5.2 (d, 1H), 7.2 (m, 4H).

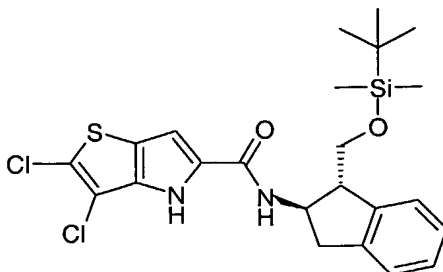
Intermediate 15: *tert*-Butyl [(1*R*,2*R*)-1-(aminocarbonyl)-2,3-dihydro-1*H*-inden-2-yl]carbamate



(1*R*,2*R*)-2-[(*tert*-butoxycarbonyl)amino]indane-1-carboxylic acid (**Intermediate 7**, 1.35 g, 4.87 mmol), 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (1.32 g, 5.36 mmol) and ammonium carbonate (1.16 g, 14.61 mmol) were dissolved in CHCl₃ (25 mL) and the mixture stirred at ambient temperature for 24h. The reaction was filtered and the volatiles removed by evaporation under reduced pressure. The crude residue was dissolved in ethyl acetate, washed with 0.5M hydrochloric acid (10 mL), water (10 mL), saturated NaHCO₃ (10 mL), brine (10 mL), dried (MgSO₄), filtered and the volatiles removed by evaporation under reduced pressure. The residue was purified by flash silica gel chromatography (1:1 iso-hexane:ethyl acetate) to give the title compound (750mg, 56%) as a colourless solid.

¹H NMR (CDCl₃) δ : 1.43(s, 9H), 2.78(dd, 1H), 3.46(dd, 1H), 3.9(m, 1H), 4.58(m, 1H), 4.95(m, 1H), 7.22(m, 4H), 7.38(m, 1H); MS m/z 299 (M+Na).

Intermediate 16: N-[(1R,2R)-1-([tert-Butyl(dimethyl)silyl]oxy)methyl]-2,3-dihydro-1H-inden-2-yl]-2,3-dichloro-4H-thieno[3,2-b]pyrrole-5-carboxamide



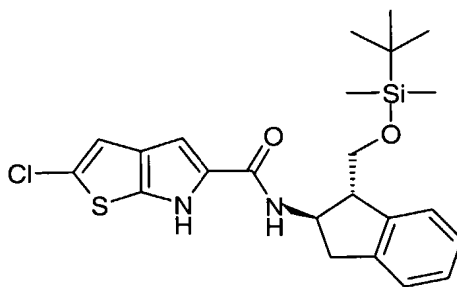
[(1R,2R)-1-([tert-Butyl(dimethyl)silyl]oxy)methyl]-2,3-dihydro-1H-inden-2-yl]amine

- 5 (Intermediate 10; 277.0 mg, 1.0 mmol), 2,3-dichloro-4H-thieno[3,2-b]pyrrole-5-carboxylic acid (Intermediate 3; 236 mg, 1.0 mmol) and DIPEA (174 μ l, 1.0 mmol) were dissolved in DCM (10 mL). HOBT (135 mg, 1 mmol) and EDCI (240 mg, 1.25 mmol) were added and the mixture stirred at ambient temperature for 2 h. The volatiles were removed under reduced pressure and the residue dissolved in ethyl acetate (25 mL), washed with water (2 x 10 mL),
10 brine (10 mL), dried (MgSO₄) and the solvent removed under reduced pressure. The crude residue was purified by flash silica gel chromatography (6:1, *iso*-hexane:ethyl acetate) to give the title compound (286 mg, 56%) as an orange foam.

¹H NMR δ : 0.03 (d, 6H), 0.85 (s, 9H), 2.9 (dd, 1H), 3.35 (m, 1H), 4.93 (m, 1H), 7.17 (s, 1H), 7.23 (m, 4H), 7.38 (m, 1H), 8.5 (d, 1H), 12.37 (s, 1H).

15

Intermediate 17: N-[(1R,2R)-1-([tert-Butyl(dimethyl)silyl]oxy)methyl]-2,3-dihydro-1H-inden-2-yl]-2-chloro-6H-thieno[2,3-b]pyrrole-5-carboxamide



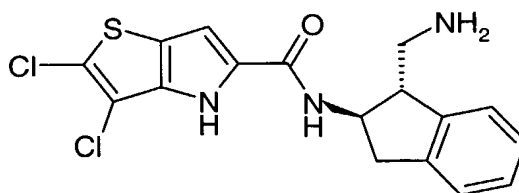
[(1R,2R)-1-([tert-Butyl(dimethyl)silyl]oxy)methyl]-2,3-dihydro-1H-inden-2-yl]amine

- 20 (Intermediate 10; 277 mg, 1.0 mmol), 2-chloro-6H-thieno[2,3-b]pyrrole-5-carboxylic acid (201 mg, 1.0 mmol) and DIPEA (174 μ l, 1.0 mmol) were dissolved in DCM (10 mL). HOBT (135 mg, 1 mmol) and EDCI (240mg, 1.25 mmol) were added and the mixture stirred at ambient temperature for 2 h. The volatiles were removed under reduced pressure and the

residue dissolved in ethyl acetate (25 mL), washed with water (2 x 10 mL), brine (10 mL), dried (MgSO₄) and the solvent removed under reduced pressure. The crude residue was purified by flash silica gel chromatography (6:1 iso-hexane:ethyl acetate) to give the title compound (320mg, 70%) as a yellow foam.

- 5 ¹H NMR δ: 0.03(d, 6H), 0.85(s, 9H), 2.9(dd, 1H), 3.35(m, 1H), 3.9(m, 2H), 4.58(m, 1H), 7.05(s, 1H), 7.2(m, 4H), 7.38(m, 1H), 8.4(d, 1H), 11.87(s, 1H).

Intermediate 18: N-[(1S,2R)-1-(Aminomethyl)-2,3-dihydro-1H-inden-2-yl]-2,3-dichloro-4H-thieno[3,2-b]pyrrole-5-carboxamide



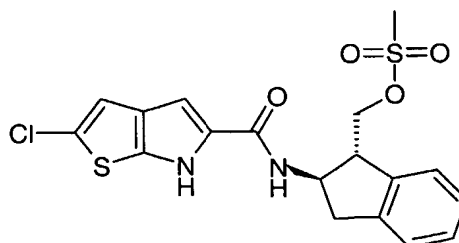
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((1R,2R)-2-[[2,3-Dichloro-4H-thieno[3,2-b]pyrrol-5-yl]carbonyl]amino)-2,3-dihydro-1H-inden-1-yl)methyl methanesulfonate (**Example 10**; 920mg, 2.0 mmol) and sodium azide (260 mg, 4.0 mmol) in dimethyl acetamide (10 mL) was heated to 60 °C for 10h, cooled, poured into ethyl acetate (50 mL), washed with water (6 x 20 mL), brine (20 mL), dried (MgSO₄)

15 filtered and evaporated. The residue was dissolved in THF, triphenylphosphine (1.05 g, 4.0 mmol) added and stirred at 60 °C for 24 h. The volatiles were removed under reduced pressure and the crude residue purified by ion exchange chromatography (Dowex 50W X2, H⁺ form; 6:1, THF:water followed by 2% ammonia in 6:1, THF:water) to give the title compound (600 mg, 79%) as a pale brown solid.

- 20 ¹H NMR δ: 2.9 (d, 2H), 2.92 (dd, 1H), 3.15 (m, 1H), 3.3 (dd, 1H), 4.6 (m, 1H), 7.15 (s, 1H), 7.2 (m, 3H), 7.3 (m, 1H), 8.48 (d, 1H), 11.8 (s, 1H); MS m/z 378, 380, 382.

Intermediate 19: ((1R,2R)-2-[(2-Chloro-6H-thieno[2,3-b]pyrrol-5-yl)carbonyl]amino)-2,3-dihydro-1H-inden-1-yl)methyl methanesulfonate

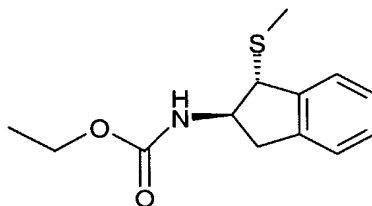


25

2-Chloro-*N*-[(1*R*,2*R*)-1-(hydroxymethyl)-2,3-dihydro-1*H*-inden-2-yl]-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide (**Example 5**; 347 mg, 1.0 mmol) and triethylamine (350 μ l, 2.5 mmol) were dissolved in THF (10 mL). Methanesulphonyl chloride (126 mg, 1.1 mmol) in THF (5 mL) was added and the mixture stirred at ambient temperature for 24 h. The volatiles were removed under reduced pressure and the residue dissolved in ethyl acetate (25 mL), washed with water (2x10 mL), brine (10 mL), dried (MgSO₄) and the solvent removed under reduced pressure to give the title compound (370 g, 87%) as a pale brown foam.

¹H NMR δ : 2.95 (dd, 1H), 3.18 (s, 3H), 3.3 (dd, 1H), 3.58 (m, 1H), 4.45 (m, 1H), 4.58 (m, 2H), 7.02 (s, 1H), 7.15 (s, 1H), 7.23 (m, 3H), 7.35 (m, 1H), 8.48 (d, 1H), 11.86 (s, 1H); MS m/z 425.1/427.1.

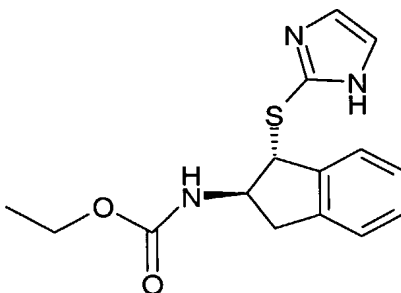
Intermediate 20: (+/-)-*trans*-Ethyl [-1-(methylthio)-2,3-dihydro-1*H*-inden-2-yl]carbamate



Sodium hydride (92 mg, 60% in oil, 2.30 mmol) was added to a solution of *trans*-ethyl (1-chloro-2,3-dihydro-1*H*-inden-2-yl)carbamate (*Bioorg.Med.Chem.Lett.* 1657–1662, **1999**; 500 mg, 2.09 mmol) in DMF (7.5 mL) at ambient temperature. The reaction was heated to 40 °C for 2 h then cooled to ambient temperature. Sodium thiomethoxide (161 mg, 2.30 mmol) was added and stirred at ambient temperature for 30 mins. The reaction was diluted with ether (50 mL) and 1M HCl (20 mL) and the organic layer was washed with saturated aqueous NaHCO₃ (20 mL), dried (MgSO₄), filtered and the volatiles removed *in vacuo*. Purification by column chromatography (eluent gradient: 1:4 to 1:2 EtOAc:hexanes) afforded the title compound (200 mg, 38%) which solidified on standing.

¹H NMR δ : 1.24 (m, 3H), 2.17 (s, 3H), 2.77 (dd, 1H), 3.50 (dd, 1H), 4.10 (m, 3H), 4.40 (m, 1H), 4.89 (br. s, 1H), 7.22 (m, 3H), 7.38 (m, 1H); MS m/z 204 [M - SMe]⁺.

Intermediate 21: (+/-)-trans-Ethyl [1-(1*H*-imidazol-2-ylthio)-2,3-dihydro-1*H*-inden-2-yl]carbamate

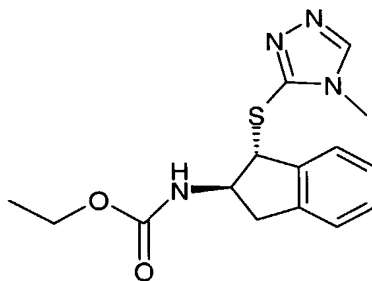


Sodium hydride (60% in oil, 84 mg, 2.08 mmol) was added to a solution of *trans*-ethyl (1-chloro-2,3-dihydro-1*H*-inden-2-yl)carbamate (*Bioorg.Med.Chem.Lett.* 1657 – 1662, **1999**; 250 mg, 1.04 mmol) in THF (7.5 mL) at ambient temperature and stirred for a further 1 h. 2-thioimidazole (104 mg, 1.04 mmol) was then added and stirred at ambient temperature for a further 1 h. The reaction was diluted with ether (50 mL) and water (20 mL) and the organic layer was dried (MgSO₄), filtered and the volatiles removed *in vacuo*. Purification by column chromatography (eluent gradient: 1:2 to 1:1 EtOAc:hexanes) afforded the title compound (170 mg, 54%) as a colourless oil.

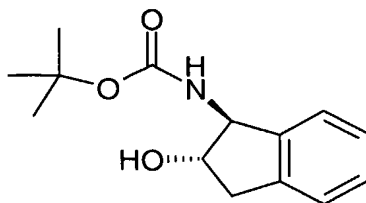
¹H NMR δ: 1.17 (t, 3H), 2.78 (dd, 1H), 3.27 (dd, 1H), 3.98 (m, 2H), 4.28 (m, 1H), 4.75 (d, 1H), 6.95 (s, 1H), 7.60 (s, 1H), 12.35 (s, 1H); MS m/z 304 [M]⁺.

The following intermediate was prepared by the method of **Intermediate 21**, using *trans*-ethyl (1-chloro-2,3-dihydro-1*H*-inden-2-yl)carbamate (*Bioorg.Med.Chem.Lett.* 1657–1662, **1999**) and 1,2,4-triazole-3-thiol.

Intermediate 22: (+/-)-trans-Ethyl {1-[(4-methyl-4*H*-1,2,4-triazol-3-yl)thio]-2,3-dihydro-1*H*-inden-2-yl}carbamate

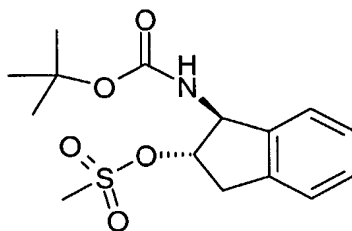


¹H NMR δ: 1.23 (t, 3H), 2.82 (dd, 1H), 3.59 (m, 4H), 4.10 (m, 2H), 4.45 (m, 1H), 5.12 (m, 1H), 5.97 (br. s, 1H), 7.25 (m, 4H), 8.17 (s, 1H), MS m/z 319 [M]⁺.

Intermediate 23: *tert*-Butyl [(1*S*,2*S*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl]carbamate

THF (100 mL) followed by 1 M sodium hydroxide was added to (1*S*,2*S*)(+)-*trans*-1-amino-2-indanol (CAS Reg. No. 163061-74-3, 5.00 g, 33.55 mmol). Di-*tert*-butyl dicarbonate (7.30 g, 33.55 mmol) was then added and stirred for 16 h. The THF was removed *in vacuo* and the remaining aqueous layer was acidified to pH 2 with citric acid (5% w/v aqueous) and diluted with EtOAc (150 mL). The organic layer was dried (MgSO₄), filtered and the volatiles removed *in vacuo*. The crude was triturated with hot ether:hexanes (1:1, 40 mL), the suspension cooled and filtered to afford the title compound (6.80 g, 81%) as a white solid.

¹H NMR δ : 1.54 (s, 9H), 2.92 (dd, 1H), 3.28 (dd, 1H), 4.23 (s, 1H), 4.42 (m, 1H), 4.93 (t, 1H), 5.03 (s, 1H), 7.22 (m, 4 H); MS m/z 313 [M+Na+MeCN]⁺.

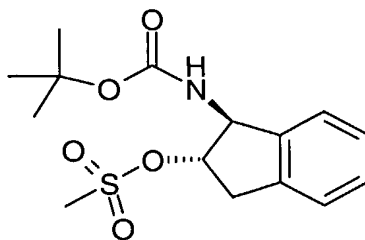
Intermediate 24: (1*S*,2*S*)-1-[(*tert*-Butoxycarbonyl)amino]-2,3-dihydro-1*H*-inden-2-yl methanesulfonate

Mesyl chloride (2.24 mL, 30.03 mmol) was added to a cooled (0 °C) solution of *tert*-butyl [(1*S*,2*S*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl]carbamate (**Intermediate 23**, 6.80 g, 27.3 mmol) and triethylamine (4.01 mL, 30.03 mmol) in DCM (100 mL) and stirred at 0 °C for 1 h. The reaction was quenched by addition of saturated aqueous NaHCO₃ (100 mL), the organic layer was dried (MgSO₄), filtered and the volatiles removed *in vacuo*. The crude product was triturated with hot ether (40 mL), cooled and filtered to afford the title compound (8.11 g, 91%) as a white solid.

¹H NMR δ : 1.45 (s, 9H), 3.18 (m, 4H), 3.47 (dd, 1H), 4.78 (s, 1H), 5.19 (m, 2H), 7.28 (m, 4 H); MS m/z 350 [M + Na]⁺.

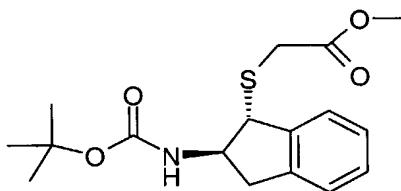
The following intermediate was prepared by the method used for **Intermediate 23** and **24** using (+/-)-*trans*-1-amino-2-indanol as the amino alcohol.

Intermediate 25: (+/-)-*trans*-1-[(*tert*-Butoxycarbonyl)amino]-2,3-dihydro-1*H*-inden-2-yl methanesulfonate



^1H NMR δ : 1.45 (s, 9H), 3.18 (m, 4H), 3.47 (dd, 1H), 4.78 (s, 1H) 5.19 (m, 2H), 7.28 (m, 4H); MS m/z 350 $[\text{M} + \text{Na}]^+$.

Intermediate 26: Methyl ((1*R*,2*R*)-2-[(*tert*-butoxycarbonyl)amino]-2,3-dihydro-1*H*-inden-1-yl)thio)acetate

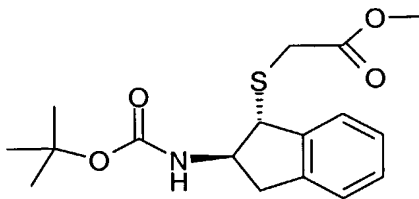


Sodium hexamethyldisilazide (NaHMDS, 10 mL, 1.0 M in THF, 10.00 mmol) was added slowly to a solution of (1*S*,2*S*)-1-[(*tert*-butoxycarbonyl)amino]-2,3-dihydro-1*H*-inden-2-yl methanesulfonate (**Intermediate 24**, 3.00g, 9.17 mmol) in THF (40 mL) ensuring the internal temperature remained <20 °C. After 30 mins methyl thioglycolate (0.90 mL, 10.00 mmol), NaHMDS (1.0 M in THF, 5 mL, 5.00 mmol) and DMF (10 mL) were added and the reaction was stirred at ambient temperature for 3 h. The reaction was quenched by the addition of water (100 mL) and ether (100 mL) and the organic layer was dried (MgSO_4), filtered and the volatiles removed *in vacuo*. Purification by column chromatography (eluent gradient: 1:4 to 1:2 EtOAc:hexanes) afforded the title compound (1.73g, 55%) as a brown oil.

^1H NMR δ : 1.43 (s, 9H), 2.75 (dd, 1H), 3.40 (d, 1H), 3.55 (m, 2H), 3.73 (s, 3H), 4.36 (m, 2H), 4.84 (s, 1H), 7.22 (m, 3H), 7.39 (m, 1H); MS m/z 360 $[\text{M} + \text{Na}]^+$.

The following intermediate was prepared by the method of (**Intermediate 26**) using (+/-)-*trans*-1-[(*tert*-butoxycarbonyl)amino]-2,3-dihydro-1*H*-inden-2-yl methanesulfonate (**Intermediate 25**) as the carbamate.

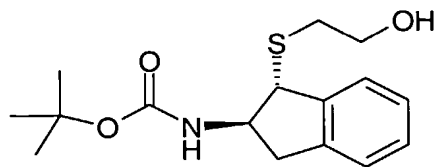
5 **Intermediate 27: (+/-)-*trans*-Methyl {(2-[(*tert*-butoxycarbonyl)amino]-2,3-dihydro-1*H*-inden-1-yl)thio}acetate**



¹H NMR δ : 1.43 (s, 9H), 2.75 (dd, 1H), 3.40 (d, 1H), 3.55 (m, 2H), 3.73 (s, 3H), 4.36 (m, 2H), 4.84 (s, 1H), 7.22 (m, 3H), 7.39 (m, 1H).

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Intermediate 28: *tert*-Butyl {(1*R*,2*R*)-1-[(2-hydroxyethyl)thio]-2,3-dihydro-1*H*-inden-2-yl}carbamate



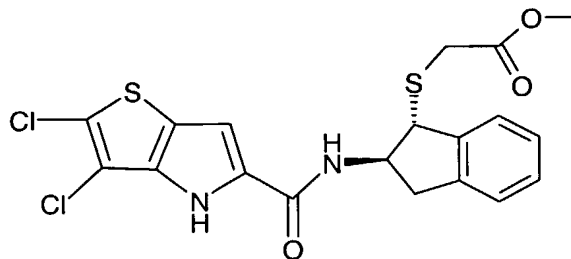
Lithium borohydride (28 mg, 1.28 mmol) was added to a solution of methyl {(1*R*,2*R*)-2-[(*tert*-butoxycarbonyl)amino]-2,3-dihydro-1*H*-inden-1-yl}thio)acetate (**Intermediate 26**, 216 mg, 0.64 mmol) in THF (5 mL) and the reaction was stirred under an argon atmosphere at ambient temperature for 5 h. A further portion of LiBH₄ (28 mg, 1.28 mmol) was added and the reaction was stirred at ambient temperature for 16 h. The reaction was quenched with aqueous ammonium chloride (20 mL) and ether (40 mL), the organic layer was dried (MgSO₄), filtered and the volatiles removed *in vacuo* to afford the title compound (196 mg, 99%) as a colourless oil.

20

¹H NMR δ : 1.43 (s, 9H), 2.75 (m, 2H), 3.03 (m, 1H), 3.55 (dd, 1H), 3.86 (m, 2H), 4.30 (s, 1H), 4.40 (m, 1H), 4.81 (s, 1H), 7.21 (m, 3H), 7.38 (m, 1H); MS *m/z* 332 [M + Na]⁺.

25

Intermediate 29: Methyl [((1*R*,2*R*)-2-[[2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrol-5-yl)carbonyl]amino]-2,3-dihydro-1*H*-inden-1-yl)thio]acetate

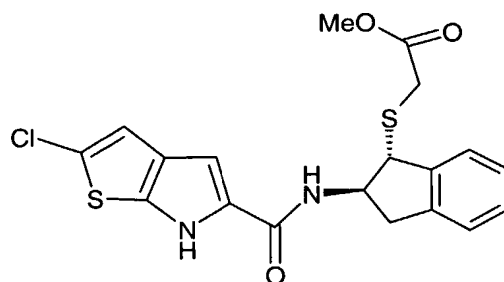


Trifluoroacetic acid (15 mL) was added to a solution of *tert*-butyl {(1*R*,2*R*)-1-[(2-hydroxyethyl)thio]-2,3-dihydro-1*H*-inden-2-yl} carbamate (**Intermediate 26**, 1.50 g, 4.45 mmol) in DCM followed by stirring at ambient temperature for 30 mins. The solvent was then removed *in vacuo* followed by re-evaporation from toluene (2 x 15 mL) followed by evaporation under high vacuum for 2 h. 5-Carboxy-2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole (**Intermediate 3**; 1.05 g, 4.45 mmol), DCM (40 mL), HOBt (681 mg, 4.45 mmol), DIPEA (2.32 mL, 13.35 mmol) and finally EDCI (1.07 g, 5.50 mmol) were added to the residue obtained from the first step and the reaction was stirred at ambient temperature for 16 h. The reaction was diluted with DCM (50 mL) then extracted with saturated aqueous NaHCO₃ (40 mL) then 1M HCl and the organic layer was dried (MgSO₄), filtered and the volatiles removed *in vacuo*. Purification by column chromatography (eluent gradient: 1:4 to 1:1 EtOAc:hexanes) afforded the title compound (1.63g, 80% over 2 steps) as a white solid.

¹H NMR δ: 2.84 (dd, 1H), 3.45 (d, 1H), 3.63 (d, 1H), 3.72 (m, 1H), 3.78 (s, 3H), 4.70 (d, 1H), 4.77 (m, 1H), 6.77 (d, 1H), 6.84 (d, 1H), 7.27 (m, 2H), 7.40 (m, 1H), 9.78 (s, 1H); MS *m/z* 477, 479 [M + Na]⁺.

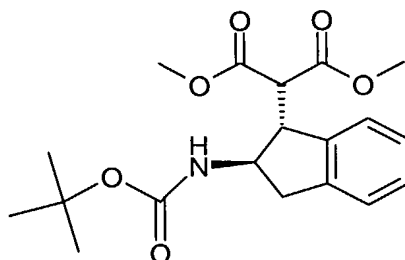
The following intermediate was made by the method of **Intermediate 29**, using (+/-)-*trans*-1-[(*tert*-butoxycarbonyl)amino]-2,3-dihydro-1*H*-inden-2-yl methanesulfonate (**Intermediate 27**) as the carbamate and 2-Chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxylic acid (**Intermediate 4**) as the acid.

Intermediate 30: (+/-)-trans-Methyl [(2-{[(2-chloro-6H-thieno[2,3-b]pyrrol-5-yl)carbonyl]amino}-2,3-dihydro-1H-inden-1-yl)thio]acetate



¹H NMR δ : 2.93 (dd, 1H), 3.35 (m, 1H), 3.55 (d, 1H), 3.58 (s, 3H), 3.70 (d, 1H), 4.43 (d, 1H),
 5 4.62 (m, 1H), 6.98 (s, 1H), 7.13 (s, 1H), 7.25 (m, 4H), 8.50 (d, 1H), 11.88 (s, 1H); MS m/z
 443, 445 [M + Na]⁺.

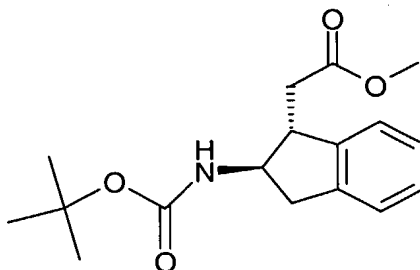
Intermediate 31: (+/-)-trans-Dimethyl {-2-[(tert-butoxycarbonyl)amino]-2,3-dihydro-1H-inden-1-yl}malonate



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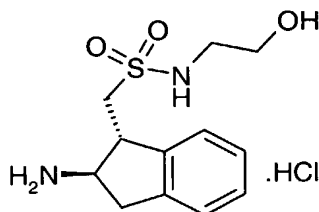
Sodium hexamethyldisilazide (1.0 M in THF, 6 mL, 6.00 mmol) was added to a stirred solution of (+/-)-trans-1-[(tert-butoxycarbonyl)amino]-2,3-dihydro-1H-inden-2-yl methanesulfonate (**Intermediate 25**, 1.79 g, 5.46 mmol) in THF (24 mL) whilst keeping the internal temperature <20 °C. After 30 mins dimethyl malonate (0.69 mL, 6.00 mmol) was
 15 added followed by NaHMDS (1.0 M in THF, 6 mL, 6.00 mmol) and the reaction was heated at 50 °C for 16 h. The reaction was cooled and then quenched with saturated aqueous ammonium chloride (50 mL) and ether (100 mL) and the aqueous layer was re-extracted with ether (50 mL) and the combined organic layers were dried (MgSO₄), filtered and the volatiles removed *in vacuo*. Purification by column chromatography (eluent gradient: 1:3 to 1:2
 20 EtOAc:hexanes) afforded the title compound (1.00 g, 50%) as a white solid after standing.
¹H NMR δ : 1.45 (s, 9H), 2.78 (dd, 1H), 3.37 (dd, 1H), 3.72 (m, 8H), 4.40 (m, 1H), 4.78 (br. s, 1H), 7.20 (m, 4H); MS m/z 386 [M + Na].

Intermediate 32: (+/-)-trans-Methyl {-2-[(*tert*-butoxycarbonyl)amino]-2,3-dihydro-1*H*-inden-1-yl}acetate



Sodium chloride (535 mg, 9.16 mmol) was added to a solution of (+/-)-*trans*-dimethyl {-2-
 5 [(*tert*-butoxycarbonyl)amino]-2,3-dihydro-1*H*-inden-1-yl}malonate (**Intermediate 31**; 830
 mg, 2.29 mmol) in DMSO (8 mL) containing 4 drops of water and the reaction was heated to
 160 °C for 5 h. The solvent was removed on a Genevac EZ-2 centrifugal evaporator and the
 residue was taken up in water (5 mL) and EtOAc (20 mL). The organic layer was dried
 (MgSO₄), filtered and evaporated. Purification by column chromatography 1:2
 10 EtOAc:hexanes afforded the title compound (500 mg, 72%) as a colourless oil.
¹H NMR (DMSO) δ: 1.45 (s, 9H), 2.78 (m, "H), 3.38 (m, 2H), 3.75 (s, 3H), 4.13 (m, 1H),
 4.87 (br. s, 1H), 7.17 (m, 4H); MS *m/z* 386 [M + Na + MeCN]⁺.

**Intermediate 33: 1-[(1*R*,2*R*)-2-Amino-2,3-dihydro-1*H*-inden-1-yl]-*N*-(2-
 15 hydroxyethyl)methanesulfonamide hydrochloride**



tert-Butyl [(1*R*,2*R*)-1-({[(2-hydroxyethyl)amino]sulfonyl}methyl)-2,3-dihydro-1*H*-inden-2-
 yl]carbamate (**Intermediate 44**, 1.25 g, 4.1 mmol) was dissolved in DCM (20 mL), HCl (4M
 in dioxane, 20 mL) was added and the solution stirred for 1 hr. The volatiles were removed *in*
 20 *vacuo*, the crude solid triturated in ether (40 mL) and filtering to afford the title compound
 (314mg, 89%) as a white solid.
¹H NMR δ: 2.94 (d, 1H), 3.11 (m, 2H), 3.47 (m, 5H), 3.75 (m, 1H), 4.07 (m, 1H), 4.88 (m,
 1H), 7.26 (m, 3H), 7.45 (m, 2H), 8.30 (bs, 3H); MS *m/z* 271.3.

The following intermediates (**34-38**) were prepared by the method of **Intermediate 33** using **Intermediates 39 to 43** as the carbamates.

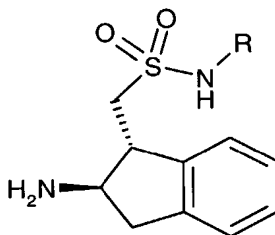
Intermediate 34: methyl *N*-([1-(1*R*,2*R*)-2-amino-2,3-dihydro-1*H*-inden-1-yl]methyl)sulfonyl)glycinate

Intermediate 35: 1-[1-(1*R*,2*R*)-2-amino-2,3-dihydro-1*H*-inden-1-yl]-*N*-(2-hydroxyethyl)methanesulfonamide

Intermediate 36: 1-[1-(1*R*,2*R*)-2-amino-2,3-dihydro-1*H*-inden-1-yl]-*N*-propylmethanesulfonamide

Intermediate 37: {1-(1*R*,2*R*)-1-[(morpholin-4-ylsulfonyl)methyl]-2,3-dihydro-1*H*-inden-2-yl}amine

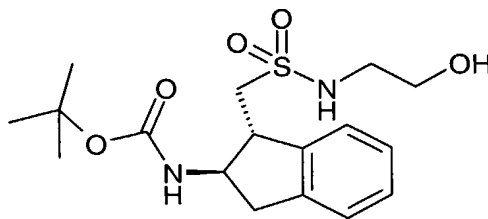
Intermediate 38: 1-[1-(1*R*,2*R*)-2-amino-2,3-dihydro-1*H*-inden-1-yl]-*N*-(2,3-dihydroxypropyl)methanesulfonamide



Intermediate	Starting material Intermediate no	R	HPLC* RT (mins)	M/z
34	39	-CH ₂ COOMe	0.68	299
35	40	-(CH ₂) ₂ OH	0.55	271
36	41	-(CH ₂) ₂ CH ₃	0.86	269
37	42	-(CH ₂) ₂ O(CH ₂) ₂	0.78	297
38	43		0.51	301

*HPLC specification: Waters 2790 Separations module, Column: Phenomenex Synergi 4u MAX-RP 8A (50x2 mm), Mobile phase: Acetonitrile:Water:Formic acid, 49.5:49.5:1, Flow rate/operating pressure: 1.1ml/min at 200psi.

Intermediate 44: *tert*-Butyl [(1*R*,2*R*)-1-({[(2-hydroxyethyl)amino]sulfonyl}methyl)-2,3-dihydro-1*H*-inden-2-yl]carbamate



tert-Butyl [(1*R*,2*R*)-1-({[(2-hydroxyethyl)amino]sulfinyl}methyl)-2,3-dihydro-1*H*-inden-2-yl]carbamate (**Intermediate 50**, 729 mg, 2.1 mmol) was dissolved in DCM (30 mL) to this was added *m*-CPBA (558 mg, 2.3 mmol) and the solution stirred for 16 hours. The solution was washed with saturated sodium bicarbonate solution (4x15 mL) and evaporated to give a white solid. The crude material was purified by flash column chromatography (SiO₂, eluent: 0-100% EtOAc/isohehexane to give the title compound (436 mg, 57%) as a white solid.

¹H NMR δ: 1.40 (s, 9H), 2.78 (m, 1H), 3.05 (m, 3H), 3.35 (m, 5H), 4.05 (m, 1H), 4.72 (t, 1H), 7.16 (m, 5H), 7.48 (m, 1H); MS *m/z* 369.1.

Intermediates 39-43 were prepared by the method used for **Intermediate 44**, using Intermediates 45 to 49 as the sulfinamide starting materials.

Intermediate 39: Methyl *N*-[({(1*R*,2*R*)-2-[(*tert*-butoxycarbonyl)amino]-2,3-dihydro-1*H*-inden-1-yl}methyl)sulfonyl]glycinate

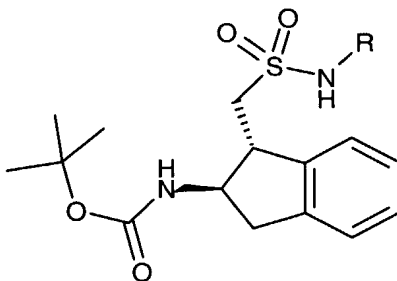
Intermediate 40: *tert*-Butyl [(1*R*,2*R*)-1-({[(2-hydroxyethyl)amino]sulfonyl}methyl)-2,3-dihydro-1*H*-inden-2-yl]carbamate

Intermediate 41: *tert*-Butyl ((1*R*,2*R*)-1-({[(propylamino)sulfonyl]methyl}-2,3-dihydro-1*H*-inden-2-yl)carbamate

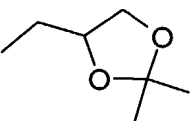
Intermediate 42: *tert*-Butyl {(1*R*,2*R*)-1-[(morpholin-4-ylsulfonyl)methyl]-2,3-dihydro-1*H*-inden-2-yl}carbamate

Intermediate 43: *tert*-Butyl {(1*R*,2*R*)-1-[({[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]amino}sulfonyl)methyl]-2,3-dihydro-1*H*-inden-2-yl}carbamate

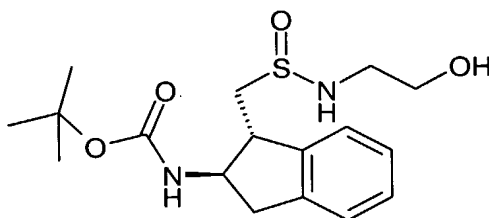
- 105 -



Intermediate	SM Intermediate	R	¹ H NMR (CDCl ₃)	M/z
39	45	-CH ₂ COOMe	1.4 (s, 9H), 2.8 (dd, 1H), 3.4 (m, 2H), 3.5 (dd, 1H), 3.8 (m, 4H), 4.0 (m, 2H), 4.8 (m, 1H), 4.9 (m, 1H), 6.9 (m, 1H), 7.2 (m, 4H)	421 (M+Na)
40	46	-(CH ₂) ₂ OH	1.4 (s, 9H), 2.7 (m, 2H), 3.3(d, 2H), 3.4 (m, 3H), 3.6 (m, 1H), 3.8 (m, 2H), 4.5 (m, 1H), 4.9 (m, 1H), 6.4 (m, 1H), 7.2 (m, 3H), 7.3 (m, 1H)	393 (M+Na)
41	47	-(CH ₂) ₂ CH ₃	1.0 (t, 3H), 1.4 (s, 9H), 1.6 (q, 2H), 2.8 (dd, 1H), 3.1 (q, 2H), 3.2 (m, 2H), 3.4 (dd, 1H), 3.6 (m, 1H), 4.5 (m, 1H), 4.8 (d, 1H), 6.2 (m, 1H), 7.2 (m, 3H), 7.3 (m, 1H)	391 (M+Na)
42	48	-(CH ₂) ₂ O(CH ₂) ₂ -	1.4 (s, 9H), 2.8 (dd, 1H), 3.3 (m, 6H), 3.5 (m, 2H), 3.8 (d, 2H), 4.25(m, 1H), 4.6 (m, 1H), 7.2 (m, 3H), 7.5 (m, 1H)	419 (M+Na)

43	49		1.3 (m, 3H), 1.4 (m, 12H), 2.7 (dd, 1H), 3.1-3.3(m, 4H), 3.4 (dd, 1H), 3.6 (m, 1H), 3.8 (m, 1H), 4.1 (t, 1H), 4.3 (q, 1H), 4.5 (m, 1H), 4.9 (m, 1H), 6.5 (m, 1H), 7.2 (m, 3H), 7.3 (m, 1H)	463 (M+Na)
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Intermediate 50: *tert*-Butyl [(1*R*,2*R*)-1-({(2-hydroxyethyl)amino}-(*R/S*)-sulfinyl)methyl]-2,3-dihydro-1*H*-inden-2-yl]carbamate



5

S-({(1*R*,2*R*)-2-[(*tert*-Butoxycarbonyl)amino]-2,3-dihydro-1*H*-inden-1-yl)methyl)ethanethioate (**Intermediate 51**, 1.19 g, 3.7 mmol) was dissolved in DCM (20 mL) and cooled to -10 °C before addition of acetic anhydride (0.35 mL, 3.7 mmol) and thionyl chloride (SO₂Cl₂) (0.60 mL, 7.4 mmol). The solution was stirred for 1 hour, the solvents were removed by evaporation, then the resultant solid was dissolved in DCM (20 mL) before addition of ethanolamine (0.45 mL, 7.4 mmol). The reaction was stirred for 16 hours before the supernatant was purified by flash column chromatography on silica gel (eluent: 0-10% MeOH in DCM) to give the title compound (739 mg, 56%) as a white solid.

10

¹H NMR δ: 1.40 (s, 9H), 2.75 (m, 1H), 3.05 (m, 5H), 3.48 (m, 2H), 4.06 (m, 1H), 4.64 (m, 1H), 6.07 (m, 1H), 7.22 (m, 6H); MS *m/z* 355.1.

15

Intermediates 45-49 were prepared by the method of **Intermediate 50**, using **Intermediate 51** as the thioester and the appropriate commercially available amine.

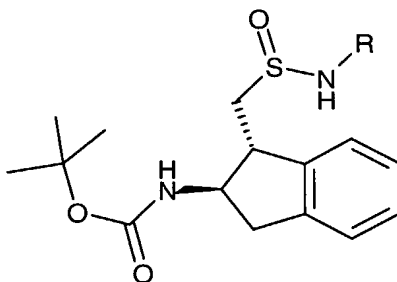
Intermediate 45: Methyl *N*-[({(1*R*,2*R*)-2-[(*tert*-butoxycarbonyl)amino]-2,3-dihydro-1*H*-inden-1-yl)methylsulfinyl]glycinate

Intermediate 46: *tert*-Butyl [(1*R*,2*R*)-1-({[(2-hydroxyethyl)amino]sulfinyl)methyl}-2,3-dihydro-1*H*-inden-2-yl]carbamate

5 **Intermediate 47: *tert*-Butyl ((1*R*,2*R*)-1-[(propylamino)sulfinyl)methyl]-2,3-dihydro-1*H*-inden-2-yl)carbamate**

Intermediate 48: *tert*-Butyl {(1*R*,2*R*)-1-[(morpholin-4-ylsulfinyl)methyl]-2,3-dihydro-1*H*-inden-2-yl}carbamate

10 **Intermediate 49: : *tert*-Butyl {(1*R*,2*R*)-1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methylamino]sulfinyl)methyl}-2,3-dihydro-1*H*-inden-2-yl}carbamate**

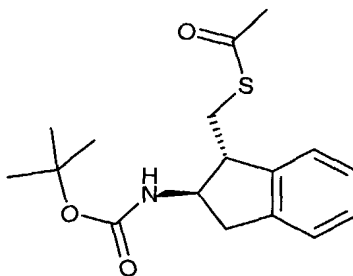


Intermediate	R	¹ H NMR	M/z
45	-CH ₂ COOMe	CDCl₃ : 1.4 (s, 9H), 2.8 (dd, 1H), 3.1 (m, 2H), 3.3 (dd, 1H), 3.5 (m, 1H), 3.7 (s, 3H), 3.8 (m, 1H), 4.0 (m, 1H), 4.3 (m, 1H), 4.8 (m, 1H), 4.9 (m, 1H), 7.2 (m, 4H)	405 (M+Na)
46	-(CH ₂) ₂ OH	d₆DMSO : 1.4 (s, 9H), 2.7 (m, 1H), 3.0 (m, 5H), 3.5 (m, 2H), 4.0 (m, 1H), 4.6 (m, 1H), 6.0 (m, 1H), 7.2 (m, 4H), 7.25 (m, 1H)	377 (M+Na)
47	-(CH ₂) ₂ CH ₃	CDCl₃ : 0.9 (t, 3H), 1.4 (s, 9H), 1.6 (q, 2H), 2.8 (dd, 1H), 3.1 (m, 4H), 3.3 (m, 1H), 3.5 (m, 1H), 4.3 (m, 1H), 4.9 (m, 1H), 7.2 (m, 3H), 7.3 (m, 1H)	375 (M+Na)
48	-(CH ₂) ₂ O(CH ₂) ₂ -	-	403 (M+Na)

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49		CDCl₃ : 1.3 (m, 3H), 1.4 (m, 12H), 2.7 (dd, 1H), 3.0 (m, 2H), 3.3(m, 4H), 3.4 (m, 1H), 3.7 (m, 1H), 4.0 (m, 1H), 4.2 (m, 2H), 4.9 (m, 1H), 7.2 (m, 3H), 7.3 (m, 1H)	447 (M+Na)
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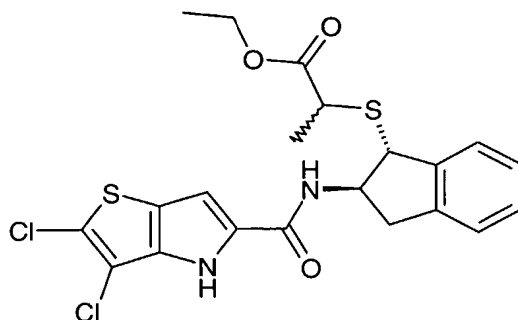
Intermediate 51: S-({(1*R*,2*R*)-2-[(*tert*-Butoxycarbonyl)amino]-2,3-dihydro-1*H*-inden-1-yl}methyl) ethanethioate



- 5 {(1*R*,2*R*)-2-[(*tert*-Butoxycarbonyl)amino]-2,3-dihydro-1*H*-inden-1-yl}methyl
methanesulfonate (1.314 g, 3.85 mmol) in DMF (10 mL) was added to a solution of thioacetic
acid (351 mg, 4.62 mmol) and caesium carbonate (813 mg, 2.5 mmol) in DMF (30 mL). The
solution was stirred at ambient temperature for 16 h then filtered. Water (20 mL) and ethyl
acetate (100 mL) were added, the organic layer was separated, washed with water (20 mL) and
10 brine (20 mL), dried (MgSO₄), filtered and evaporated. The residue was purified by column
chromatography (eluent: EtOAc:toluene, 1:19) to afford the title compound (919 mg, 75%) as
an oil which crystallised on standing.

¹H NMR (CDCl₃) δ: 1.4 (s, 9H), 2.4 (s, 3H), 2.8 (dd, 1H), 3.2 (m, 3H), 3.3 (dd, 1H), 4.1 (m, 1H), 4.8 (m, 1H), 7.2 (m, 3H), 7.3 (m, 1H).

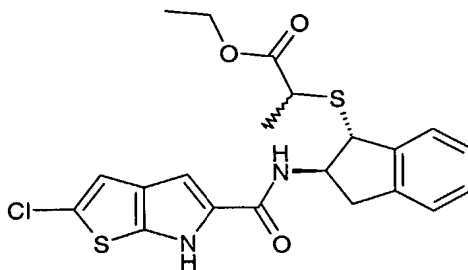
Intermediate 52:: Ethyl (2R/S)-[(((1R,2R)-2-[[2,3-Dichloro-4H-thieno[3,2-b]pyrrol-5-yl)carbonyl]amino}-2,3-dihydro-1H-inden-1-yl)thio]propanoate



This intermediate was made by an analogous process to that used for Intermediate 29.

- 5 ¹H NMR δ: 1.12 (t, 3H), 1.39 (dd, 3H), 2.94 (dt, 1H), 3.39 (m, 1H), 4.00 (m, 3H), 4.52 (dd, 1H), 4.69 (m, 1H), 7.12 (s, 1H), 7.26 (m, 4H), 8.59 (dd, 1H); MS m/z 483.1.

Intermediate 53: Ethyl (2R/S)-[(((1R,2R)-2-[[2-chloro-6H-thieno[2,3-b]pyrrol-5-yl)carbonyl]amino}-2,3-dihydro-1H-inden-1-yl)thio]propanoate



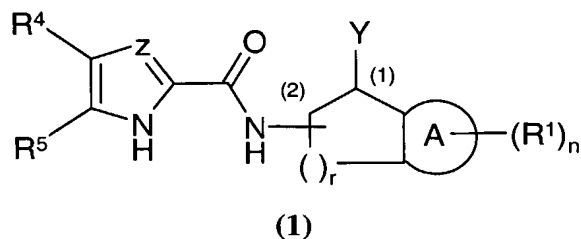
10

This intermediate was made by an analogous process to that used for Intermediate 29.

¹H NMR δ: 1.12 (t, 3H), 1.39 (dd, 3H), 2.94 (dt, 1H), 3.39 (m, 1H), 4.00 (m, 3H), 4.52 (dd, 1H), 4.66 (m, 1H), 7.01 (s, 1H), 7.12 (s, 1H), 7.26 (m, 4H), 8.50 (dd, 1H); MS m/z 449.2

Claims

1. A compound of formula (1):



wherein:

Z is CH or nitrogen;

R⁴ and R⁵ together are either -S-C(R⁶)=C(R⁷)- or -C(R⁷)=C(R⁶)-S-;

R⁶ and R⁷ are independently selected from hydrogen, halo, nitro, cyano, hydroxy,

10 fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy and (1-4C)alkanoyl;

A is phenylene or heteroarylene;

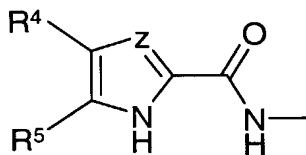
n is 0, 1 or 2;

R¹ is independently selected from halo, nitro, cyano, hydroxy, carboxy, carbamoyl,

15 N-(1-4C)alkylcarbamoyl, N,N-((1-4C)alkyl)₂carbamoyl, sulphamoyl, N-(1-4C)alkylsulphamoyl, N,N-((1-4C)alkyl)₂sulphamoyl, -S(O)_b(1-4C)alkyl (wherein b is 0,1, or 2), -OS(O)₂(1-4C)alkyl, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, (1-4C)alkanoyl, (1-4C)alkanoyloxy, hydroxy(1-4C)alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy and -NHSO₂(1-4C)alkyl;

20 or, when n is 2, the two R¹ groups, together with the carbon atoms of A to which they are attached, may form a 4 to 7 membered saturated ring, optionally containing 1 or 2 heteroatoms independently selected from O, S and N, and optionally being substituted by one or two methyl groups;

r is 1 or 2; and when r is 1 the group



25

is a substituent on carbon (2) and when r is 2 (hereby forming a six membered ring) the same group is a substituent on carbon (2) or on carbon (3);

- Y is selected from $-C(O)R^2$, $-C(O)OR^2$, $-C(O)NR^2R^3$, $-(1-4C)alkyl$ [optionally substituted by 1 or 2 substituents independently selected from hydroxy, $-C=NR^2$, $(1-4C)alkoxy$, aryloxy, heterocycloxy, $-S(O)_bR^2$ (wherein b is 0, 1 or 2), $-O-S(O)_bR^2$ (wherein b is 0, 1 or 2), $-NR^2R^3$, $-N(OH)R^2$, $-NR^2C(=O)R^2$, $-NHOHC(=O)R^2$, $-SO_2NR^2R^3$, $-N(R^2)SO_2R^2$, aryl and heterocyclyl], $-C(O)NOH$, $-C(O)NSH$, $-C(N)OH$, $-C(N)SH$, $-SO_2H$, $-SO_3H$, $-SO_2N(OH)R^2$, $-(2-4C)alkenyl$, $-SO_2NR^2R^3$, $-(1-4C)alkylC(O)R^2$, $-(1-4C)alkylC(O)OR^2$, $-(1-4C)alkylSC(O)R^2$, $-(1-4C)alkylOC(O)R^2$, $-(1-4C)alkylC(O)NR^2R^3$, $-(1-4C)alkylOC(O)OR^2$, $-(1-4C)alkylN(R^2)C(O)OR^2$, $-(1-4C)alkylN(R^2)C(O)NR^2R^3$, $-(1-4C)alkylOC(O)NR^2R^3$, $(3-6C)cycloalkyl$ (optionally substituted by 1 or 2 R^8), aryl, heterocyclyl (wherein the heterocyclic ring is linked by a ring carbon atom), $-(1-4C)alkylSO_2(2-4C)alkenyl$ and $-S(O)_cR^2$ (wherein c is 0, 1 or 2); R^2 and R^3 are independently selected from hydrogen, $-O(1-4C)alkyl$, $-S(1-4C)alkyl$, $-N(1-4C)alkyl$, heterocyclyl, aryl, and $(1-4C)alkyl$ [optionally substituted by 1 or 2 R^8 groups]; or
- wherein NR^2R^3 may form a 4 to 7 membered saturated, partially saturated or unsaturated ring, optionally containing 1, 2 or 3 additional heteroatoms independently selected from N, O and S (provided there are no O-O, O-S or S-S bonds), wherein any $-CH_2-$ may optionally be replaced by $-C(=O)-$, and any N or S atom may optionally be oxidised to form an N-oxide or SO or SO_2 group respectively, and wherein the ring is optionally substituted by 1 or 2 substituents independently selected from halo, cyano, $(1-4C)alkyl$, hydroxy, $(1-4C)alkoxy$ and $(1-4C)alkylS(O)_b-$ (wherein b is 0, 1 or 2); R^8 is independently selected from hydrogen, hydroxy, $(1-4C)alkyl$, $(2-4C)alkenyl$, $(1-4C)alkoxy$, cyano((1-4C))alkyl, amino((1-4C))alkyl [optionally substituted on nitrogen by 1 or 2 groups selected from $(1-4C)alkyl$, hydroxy, hydroxy((1-4C))alkyl, dihydroxy((1-4C))alkyl, $-CO_2(1-4C)alkyl$, aryl and aryl((1-4C))alkyl], halo((1-4C))alkyl, dihalo((1-4C))alkyl, trihalo((1-4C))alkyl, hydroxy((1-4C))alkyl, dihydroxy((1-4C))alkyl, $(1-4C)alkoxy(1-4C)alkoxy$, $(1-4C)alkoxy(1-4C)alkyl$, hydroxy(1-4C)alkoxy, 5- and 6-membered cyclic acetals and mono- and di-methyl derivatives thereof, aryl, heterocyclyl, (heterocyclyl)(1-4C)alkyl, $(3-7C)cycloalkyl$ (optionally substituted with 1 or 2 hydroxy groups, $(1-4C)alkyl$ or $-CO_2(1-4C)alkyl$), $(1-4C)alkanoyl$, $(1-4C)alkylS(O)_b-$ (wherein b is 0, 1 or 2), $(3-6C)cycloalkylS(O)_b-$ (wherein b is 0, 1 or 2), arylS(O)_b- (wherein b is 0, 1 or 2), heterocyclylS(O)_b- (wherein b is 0, 1 or 2), benzylS(O)_b- (wherein b is 0, 1 or 2),

(1-4C)alkylS(O)_c(1-4C)alkyl- (wherein c is 0, 1 or 2), -N(OH)CHO, -C(=N-OH)NH₂,
 -C(=N-OH)NH(1-4C)alkyl, -C(=N-OH)N((1-4C)alkyl)₂, -C(=N-OH)NH(3-6C)cycloalkyl,
 -C(=N-OH)N((3-6C)cycloalkyl)₂, -COCOOR⁹, -C(O)N(R⁹)(R¹⁰), -NHC(O)R⁹,
 -C(O)NHSO₂((1-4C)alkyl), -NHSO₂R⁹, (R⁹)(R¹⁰)NSO₂-, -COCH₂OR¹¹, -COCH₂OH,
 5 (R⁹)(R¹⁰)N-, -COOR⁹, -CH₂OR⁹, -CH₂COOR⁹, -CH₂OCOR⁹, -CH₂CH(CO₂R⁹)OH, -
 CH₂C(O)NR⁹R¹⁰, -(CH₂)_wCH(NR⁹R¹⁰)CO₂R^{9'} (wherein w is 1, 2 or 3), and
 -(CH₂)_wCH(NR⁹R¹⁰)CO(NR^{9'}R^{10'}) (wherein w is 1, 2 or 3) ;

R⁹, R^{9'}, R¹⁰ and R^{10'} are independently selected from hydrogen, hydroxy, (1-4C)alkyl
 (optionally substituted by 1 or 2 R¹¹), (2-4C)alkenyl, (3-7C)cycloalkyl (optionally substituted
 10 by 1 or 2 hydroxy groups), cyano((1-4C))alkyl, trihaloalkyl, aryl, heterocyclyl,
 heterocyclyl((1-4C)alkyl), -CO₂(1-4C)alkyl; or

R⁹ and R¹⁰ together with the nitrogen to which they are attached, and/or R^{9'} and R^{10'} together
 with the nitrogen to which they are attached, form a 4- to 6-membered ring where the ring is
 optionally substituted on carbon by 1 or 2 substituents independently selected from oxo,
 15 hydroxy, carboxy, halo, nitro, cyano, carbonyl, (1-4C)alkoxy and heterocyclyl; or the ring may
 be optionally substituted on two adjacent carbons by -O-CH₂-O- to form a cyclic acetal
 wherein one or both of the hydrogens of the -O-CH₂-O- group may be replaced by a methyl;
 R¹¹ is independently selected from (1-4C)alkyl and hydroxy(1-4C)alkyl;
 or a pharmaceutically acceptable salt or pro-drug thereof.

20

2. A compound of the formula (1), or a pharmaceutically acceptable salt or pro-drug
 thereof, as claimed in claim 1, wherein A is phenylene.

3. A compound of the formula (1), or a pharmaceutically acceptable salt or in-vivo
 25 hydrolysable ester thereof, as claimed in claim 1 or claim 2, wherein n is 0.

4 A compound of the formula (1), or a pharmaceutically acceptable salt or in-vivo
 hydrolysable ester thereof, as claimed in any one of the preceding claims wherein r is 1.

30 5. A compound of the formula (1), or a pharmaceutically acceptable salt or in-vivo
 hydrolysable ester thereof, as claimed in any one of the preceding claims wherein R⁶ and R⁷
 are independently hydrogen or halo.

6. A compound of the formula (1), or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof, as claimed in any one of the preceding claims wherein Y is selected from $-C(O)OR^2$, $-C(O)NR^2R^3$, $-(1-4C)alkyl$ [optionally substituted by a substituent selected from hydroxy, $(1-4C)alkoxy$, $-S(O)_bR^2$ (wherein b is 0, 1 or 2), $-O-S(O)_bR^2$ (wherein b is 0, 1 or 2), $-NR^2R^3$, $-NR^2C(=O)R^2$ and $-SO_2NR^2R^3$], $-(1-4C)alkylC(O)R^2$, $-(1-4C)alkylC(O)OR^2$, $-(1-4C)alkylOC(O)R^2$, $-(1-4C)alkylC(O)NR^2R^3$, $-(1-4C)alkylOC(O)OR^2$, $-(1-4C)alkylN(R^2)C(O)OR^2$, $-(1-4C)alkylN(R^2)C(O)NR^2R^3$, $-(1-4C)alkylSC(O)R^2$, $-(1-4C)alkylOC(O)NR^2R^3$, $-(1-4C)alkylSO_2(2-4C)alkenyl$ and $-SO_cR^2$ (wherein c is 0, 1 or 2).

10

7. A compound of the formula (1), or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof, as claimed in any one of the preceding claims wherein R^2 and R^3 are independently selected from hydrogen, heterocyclyl, $-O(1-4C)alkyl$, $-N(1-4C)alkyl$, $(1-4C)alkyl$ [optionally substituted by 1 or 2 R^8 groups]; or an NR^2R^3 group forms a morpholine, thiomorpholine (and oxidised versions thereof), pyrrolidine, or piperidine ring and wherein the ring is optionally substituted by 1 or 2 substituents independently selected from chloro, fluoro, hydroxy and methoxy.

15

8. A compound of the formula (1), or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof, as claimed in any one of the preceding claims wherein R^8 is independently selected from hydrogen, hydroxy, $-C(O)N(R^9)(R^{10})$, $-NHC(O)R^9$, $-COOR^9$, $-CH_2OR^9$, $-CH_2COOR^9$, $-CH_2OCOR^9$, aryl, heterocyclyl, and 5- and 6-membered cyclic acetals and mono- and di-methyl derivatives thereof.

20

9. A compound of the formula (1), or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof, as claimed in any one of the preceding claims wherein R^9 and R^{10} are independently selected from hydrogen, hydroxy and $(1-4C)alkyl$ or R^9 and R^{10} together with the nitrogen to which they are attached form a morpholine, thiomorpholine (and oxidised versions thereof), pyrrolidine, or piperidine ring.

25

10. A pharmaceutical composition which comprises a compound of the formula (1), or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof, as claimed in claim 1 in association with a pharmaceutically-acceptable diluent or carrier.

30

11. A compound of the formula (1), or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof, as claimed in claim 1, for use in a method of treatment of a warm-blooded animal such as man by therapy.

5 12. A compound of the formula (1), or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof, as claimed in claim 1, for use as a medicament.

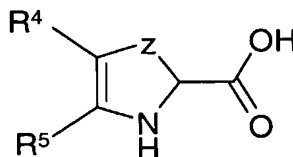
13. A compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as claimed in claim 1, for use as a medicament in the treatment of
10 type 2 diabetes, insulin resistance, syndrome X, hyperinsulinaemia, hyperglucagonaemia, cardiac ischaemia or obesity in a warm-blooded animal such as man.

14. The use of a compound of the formula (1), or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof, as claimed in claim 1, in the manufacture of a medicament for
15 use in the treatment of type 2 diabetes, insulin resistance, syndrome X, hyperinsulinaemia, hyperglucagonaemia, cardiac ischaemia or obesity in a warm-blooded animal such as man.

15. The use of a compound of the formula (1), or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof, as claimed in claim 1, in the manufacture of a medicament for
20 use in the treatment of type 2 diabetes in a warm-blooded animal such as man.

16. A process for the preparation of a compound of formula (1) as claimed in claim 1, which process comprises:

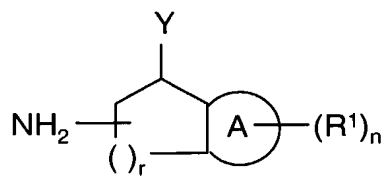
reacting an acid of the formula (2):



(2)

or an activated derivative thereof; with an amine of formula (3):

- 115 -



(3)

and thereafter if necessary:

- i) converting a compound of the formula (1) into another compound of the formula (1);
- 5 ii) removing any protecting groups;
- iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

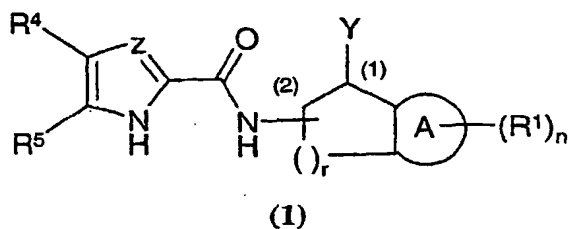
INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB2004/003345

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

A compound of the formula (1) or a pharmaceutically-acceptable salt, or pro-drug thereof;



wherein, for example,

Z is CH or nitrogen;

R⁴ and R⁵ together are either -S-C(R⁶)=C(R⁷)- or -C(R⁷)=C(R⁶)-S-;

R⁶ and R⁷ are independently selected from hydrogen, halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, carboxy and carbamoyl;

A is phenylene or heteroarylene;

n is 0, 1 or 2;

r is 1 or 2;

R¹ is halo, cyano or carboxy;

Y is selected from -C(O)R², -C(O)OR², -C(O)NR²R³, -(1-4C)alkyl [optionally substituted] -(2-4C)alkenyl, -SO₂NR²R³, and -S(O)_cR² (wherein c is 0, 1 or 2);

R² and R³ are independently selected from hydrogen, -O(1-4C)alkyl, -S(1-4C)alkyl, -N(1-4C)alkyl, heterocyclyl, aryl, and (1-4C)alkyl [optionally substituted];

possess glycogen phosphorylase inhibitory activity and accordingly have value in the treatment of disease states associated with increased glycogen phosphorylase activity.

Processes for the manufacture of compounds and pharmaceutical compositions containing them are described.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2004/003345

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/407 C07D495/04 A61P3/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 02/20530 A (FREEMAN SUE ; KENNY PETER (GB); MORLEY ANDREW (GB); WHITTAMORE PAUL (G) 14 March 2002 (2002-03-14) page 36, line 25 - page 39, line 30; examples 112,133-140,142,148-154 -----	1-16
Y	EP 1 136 071 A (PFIZER PROD INC) 26 September 2001 (2001-09-26) the whole document -----	1-16
P,A	WO 03/074531 A (WHITTAMORE PAUL ROBERT OWEN ; SIMPSON IAIN (GB); ASTRAZENECA UK LTD (G) 12 September 2003 (2003-09-12) -----	1-16

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

24 September 2004

Date of mailing of the international search report

06/10/2004

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Gavriliu, D

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB2004/003345

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0220530	A	14-03-2002	AT 263772 T	15-04-2004
			AU 8283301 A	22-03-2002
			BG 107624 A	30-01-2004
			BR 0113606 A	24-06-2003
			CA 2417594 A1	14-03-2002
			CN 1473163 T	04-02-2004
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